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THE PIONEER IN GYNECOLOGICAL RADIOTHERAPY
AND THE FAITHFUL FRIEND
BY PUPILS AND COLLEAGUES ALL OVER THE WORLD TO
CELEBRATE HIS SIXTY-FIFTH ANNIVERSARY, NOVEMBER
THE THIRTEENTH, 1947, AND AS AN EXPRESSION OF
DEEP GRATITUDE AND ADMIRATION, ON THE
OCCASION OF HIS RETIRING FROM THE
CHIEFSHIP OF THE GYNECOLOGICAL
DEPARTMENT OF THE
RADIUMHEMMET
STOCKHOLM

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JAMES HEYMAN

ON HIS SIXTY-FIFTH ANNIVERSARY

November 13th, 1947

JAMES HEYMAN was born on November 13th, 1882, in Gothenburg. His medical studies were pursued at Uppsala University where he qualified as Licentiate of Medicine in 1912. Of significance for his future activities in the anti-cancer campaign were the three years during which he as medical student served as assistant at the Pathological-anatomical Institution of the University under the leadership of the eminent authorities on tumor pathology, ULRIK QUENSEL and ARTUR VESTBERG.

After internships in surgical clinics during the years of 1912 and 1913 HEYMAN specialized in gynecology and obstetrics at the Caroline Institute in Stockholm from 1914 to 1918 under the outstanding teachers and physicians HJALMAR FORSSNER and ERIK AHLSTRÖM, both of whom were eminent supporters of radiotherapy. He was in 1918 appointed Associate Professor in these subjects. For several years he taught the University courses of gynecology and obstetrics.

HEYMAN's interest was early directed towards gynecological radiotherapy. Parallel with his service within gynecology at the University Clinics he was from December 1, 1914, to December 31, 1915, appointed Assistant Physician at the general department of the Radiumhemmet, thus gaining increasing experience in the various branches of radiotherapy in this period of hectic development.

On January 1, 1916, HEYMAN was appointed Director for the small special department for gynecological radiotherapy then set up at the Radiumhemmet, which he during three decades of activity has developed to an internationally known center for radiotherapy in gynecology. In the year of 1938 the Swedish Government at the instance of the entire body of Professors of Gynecology of the medical faculties of Sweden, conferred upon him a titulary Professorship.

Alongside with his work in radiotherapy HEYMAN has been successfully engaged in gynecological surgery and in obstetrics, both in the clinics and in private practice.

As will be seen from his bibliography his authorship is not restricted to radiotherapy alone, but embraces various fields of gynecology and obstetrics.

I will here limit myself mainly to HEYMAN's contributions towards the development of radiotherapy within gynecology, but will, however, commence by mentioning a few of his publications in the field of obstetrics which bear witness to the brilliant faculties of observation and the keen interest in social welfare which also distinguish his work within radiotherapy.

His investigations on *the symphysis pubis in pregnancy and parturition* which was carried out in collaboration with Dr. A. LUNDQUIST in connection with a »rupture of the symphysis» observed by HEYMAN, revealed by means of radiographic measurements that the symphysis expands during gravidity, contracting again after parturition. During partus there is no expansion of the symphysis. Instead, the enlargement of the symphysis occurs during the latter term of pregnancy as a physiological preliminary to parturition, similarly as in *e. g.* guinea-pig, in which a very marked diastasis occurs shortly before partus.

On the initiative of HEYMAN in the year of 1918 a ward for infants was by private means established at the Stockholm Maternity Hospital, with accommodations for six mothers with infants in need of hospital treatment. This has been of great importance in opening up new vistas for the care of infants in our maternity hospitals. Earlier, even ailing infants frequently were discharged without special treatment, with the result that many children died because of the lack of care.

Long before prophylactic pre-natal treatment was contemplated in this country HEYMAN in 1919 put forward a noteworthy proposition for eclampsia prophylaxis in Stockholm. Pregnant women were to leave urine samples at the pharmacies of the city and the tests for albumin were to be defrayed by public funds. In the presence of albumin the pharmacy was to report this to one of the maternity hospitals of the city, which then was to contact the patient for examination and treatment.

HEYMAN's report in the year of 1922 on *radium therapy in climacteric hemorrhage* called attention to the advantages of intrauterine radium irradiation in these conditions. He has since with great success carried out this mode of treatment as well as roentgen treatment in functional hemorrhage. His pupil, H. L. KOTTMEIER in this volume presents a report of the latest experience of the Radiumhemmet within this field of radiotherapy. Radiation therapy in myoma, preferably the roentgen treatment, has also been successfully carried out at the Radiumhemmet under HEYMAN's leadership and has been described in publications by his pupil BIRGER LUNDQUIST.

HEYMAN has thoroughly studied the *radiotherapy in ovarian cancer* and has convincingly demonstrated the value of radio-surgery in operable and border-line cases, as well as the value of radiotherapy alone in inoperable cases.

HEYMAN's main achievement, however, giving him a place of honor among the pioneers of gynecological radiotherapy, is his contribution towards *»the Stockholm method» in the radiotherapy of uterine cancer.*

What then is this »Stockholm method» of radiotherapy in uterine cancer? What is HEYMAN's contribution to the development of this method and what results has he reached? I will endeavour to answer these questions briefly.

The principles of the tumor therapy of the Radiumhemmet in Stockholm — »the Stockholm method» — were drawn up during the second decade of this century on the basis of our experience of radiotherapy in malignant growth in various sites. The principles may be summarized as follows:

A minimum dose should be given that in the individual case will weaken the tumor's energy of growth to such an extent that the organism will be able to overcome the tumor disease by a natural healing process.

The irradiation to the healthy surrounding tissues should not reach a maximum dose that would damage the local or general resistance of the body against the tumor.

The dose required should be given within the shortest time possible. In conditions such as uterine cancer, where the risk of necrosis in the tumor and of injury to the surroundings necessitate fractionated dosage, the whole treatment should be finished as soon as possible, before any lasting changes have taken place in the vessels and the connective tissues of the surroundings, resulting in lowered capacity of reaction and increased tendency to necrosis by iterated irradiation. On the other hand, however, a certain period of time, varying according to the individual circumstances, should be permitted to pass between each treatment in order that the healing process primarily instituted may be given sufficient time to reach a certain degree of development before the irradiation is repeated.

A proper technic of application must be planned to realize these principles according to the requirements of the individual case.

The technic, developed for the realization of »the Stockholm method» is in its main features characterized by a few intense treatments with coincident intrauterine and vaginal applications of radium salt in gold and platinum tubes, screened by a primary filter equivalent to 3 mm. of lead and by a secondary filter of paper and (or) rubber.

Initially, three treatments were given, each treatment of about 20

hours duration, with an interval of one week between the first and the second treatment and three weeks between the second and the third treatment, the total intrauterine dose averaging 2,400 mg hrs, and the total vaginal dose averaging about 4,500 mg hrs.

During the first decades the radium tubes in one or several cylindric containers corresponding to the length of the cervical canal were placed in the uterine cavity as well in cases of cancer of the corpus as in cervical cancer. For vaginal application the entire tumor surface is covered with radium tubes in cylindric or flat containers varying in size and number according to the case. Gauze-packing keeps the vaginal applicator in position and provides the necessary distance between the applicator and the rectum.

Supplementary roentgen irradiation has as a rule been given to the parametrium.

HEYMAN adapted the »Stockholm method» to the morphology of the pelvic organs and to the special tasks of gynecology.

Observations by HEYMAN and other authors have shown that it is not necessary to take particular consideration to the histological character of the growth in planning the treatment of the uterine cancer, as no practical difference in the results has been obtained in the treatment of various histological types of cancer.

The result of the treatment is essentially dependent of the method by which the treatment is planned and carried out with consideration to the clinical character and extent of the growth, and to the existing risk of complications.

The difficulty of keeping sufficient accommodations and radium available for the rapidly increasing number of patients forced HEYMAN to further concentrate the treatment according to the Stockholm method. Since 1932 he has been able to carry through the radium treatment in two séances in most cases without impairing the 5-year results. These treatments last for about 20 to 24 hours with an interval of three weeks, the total intrauterine dose being about 2,400 to 2,600 mg hrs and the total vaginal dose about 4,000 mg hrs.

It is, however, not sufficient merely to apply the radium according to some empiric schedule. Correct application of the radium requires considerable variation according to the individual case.

In order to be able in each individual case to adapt the technic to the local circumstances HEYMAN has in collaboration with the Physical Department of the Radiumhemmet constructed a sufficient number of radium applicators and containers of various form and size and for different radium contents. In each case the radium application is prepared and carried out with the same attention to every detail as a surgical operation.

Owing to the large selection of radium applicators the total dose is relatively rarely altered in uncomplicated cases and if so, within fairly narrow limits, but the variations may become rather significant in exceptional cases.

The irradiation time must be shortened or lengthened in order to attain the desired doses in milligramme-hours by different radium quantities. In about 45 per cent of the total number of cases treated in recent years the standard technic has been modified.

After having carried out a series of experiments with combined radium and roentgen treatment HEYMAN since 1929 gives roentgen irradiation in all cases of cervical cancer three weeks after the last radium treatment. During the last decade he has more and more combined *»brachyradium»* (radium at short distance) with *»teleradium»* treatment in advanced cases. The primary results with a consequent palliation have been decidedly better than those we were able to obtain by the method of treatment employed previously.

Of great importance is the individualization of the standard technic in cases in which the development of serious infection may be feared. HEYMAN has elaborated a valuable *»tentative» method of treatment in cervical cancer complicated by inflammatory conditions* and has invented special instruments and applicators for the local application of larger quantities of radium during a short time.

HEYMAN has proved that in cases of acute salpingitis complicating a uterine cancer a radical operation followed by the application of radium to the cancer as soon as possible is the correct procedure. Nine out of eleven patients submitted to a bilateral salpingo-oophorectomy prior to radiotherapy of a cervical cancer were alive and without evidence of the disease five years after the treatment.

In cervical cancer coexistent with pregnancy HEYMAN has since 1932 successfully administered the standard radium treatment in spite of the pregnancy after having with poor results tried various other methods such as cesarian section, Wertheim's operation, vaginal hysterectomy or induced abortion followed by post-operative irradiation. Sixteen (or 57 per cent) out of twenty-eight cases are alive and free of symptoms of cancer five years after a radium treatment followed by spontaneous abortion or premature birth. Only in case of a viable foetus has a Porro operation and post-operative irradiation been advised.

The possibilities of avoiding radiation injuries in the radiotherapy of the uterine cancer have been the object of HEYMAN's unremitting interest and his pupil AXEL INGELMAN-SUNDBERG has this year in a supplementary volume to the Acta Radiologica presented the Radiumhemmet's experience on this subject.

A considerable improvement is noticeable in the results of radio-

logical treatment of cervical cancer at Radiumhemmet during the two last decades, since HEYMAN has more and more realized his principles of the individualized treatment within the compass of the Stockholm method.

Radiumhemmet now disposes of 4,611 cases of cervical cancer treated during the period 1914 to 1941 inclusive and observed at least five years after the beginning of the treatment.

For the period 1914 to 1931 inclusive an average absolute cure rate (*i. e.* the proportion of patients apparently cured at least five years as a percentage of the total number examined with a view to treatment) of 21.6 per cent was obtained (2,104 patients treated) whereas in *1932 to 1941* inclusive the corresponding average was *31.9 per cent.* The »*stage rate*» (*i. e.* the proportion of cured patients expressed as a percentage of the total number in that stage actually treated) has augmented in all stages.

The stage rate has increased in *stage I* (the tumor limited to the cervix) from 52.4 per cent to *69.3* per cent; *in stage II* (the tumor extending into the vaults with or without involvement of the parametrium with the uterus still movable) from 34.7 per cent to *46.5* per cent and in *stage III* (at least one parametrium massively infiltrated) from 15.6 per cent to *21.1* per cent. The value of this progress is perhaps most evident if we consider that the cure rate in stage III in the latter period attains about the same figure as the absolute cure rate for the whole material in the former period.

Already in 1927 HEYMAN was able to prove that with due regard to the much higher percentage of inoperable cases in the initial material the radiotherapy according to the Stockholm method, with an absolute cure rate of at least 20.7 per cent, was superior to the operative treatment of cervical cancer in respect to the average absolute results (20.2 per cent) in the eleven best operation statistics.

The above cited results at the Radiumhemmet during the last decade, as compared with hitherto published surgical statistics, evidently show that now radiotherapy is superior to surgery also in clinically operable cases of cervical cancer.

Even if HEYMAN's cure rate has not been attained, the development throughout the world has had the same trend. The surgical treatment is now used only exceptionally as exclusive treatment in cervical cancer.

Although it has been established that surgery alone is clearly inferior to radiotherapy alone in cervical cancer it has in many quarters nevertheless been tried to still employ surgery as principle intervention, but combined with pre-operative irradiation with a view to improve the results obtained by operative treatment alone.

Considering the number of clinics in different parts of the world

hich for many years have used the pre-operative irradiation it is, how-er, surprising that only occasional results are still presented in order demonstrate the advantages of the method without being able to ove the superiority of prophylactic hysterectomy.

HEYMAN has thoroughly studied the possibilities of improving the sults in the treatment of operable cases of cervical cancer by a com-nation of surgery and radiotherapy. In a thorough analysis of the adiumhemmet series he has shown that an improvement of the re-lts cannot be expected by combining surgey with pre-operative ir-diation. The number of patients lost at routine prophylactic hyster-tomy will probably exceed those saved by the operation.

In a combined treatment radiotherapy in cervical cancer as principle and primary intervention has a definite advantage above surgery, not only because its superiority with regard to the final results is established but also because in the hand of an expert radiologist the risk and inconvenience to the patient are considerably less than those caused by surgery.

A primary healing, *i. e.* clinical freedom from symptoms, obtained by radiotherapy in cervical cancer is at least fully as permanent as if the healing had been obtained by an extensive operation. On the other hand, however, a local recurrence in a patient primarily cured by radiotherapy can as a rule not be cured by additional radium treatment.

Hysterectomy or electroendothermy have again proved to be of great value as a complementary treatment in local recurrences after radiological healing. Of 96 patients operated upon at the Radiumhemmet because of local recurrence after radiological healing 26 (27.1 per cent) were alive five years after the operation.

According to my opinion one of HEYMAN's most outstanding contributions to the cancer therapy is that he has analyzed the basis for a combined radiological-surgical treatment in cancer of the uterus and has given convincing evidence that our present experience justifies the rule he has propounded: radiotherapy as a principle, primary and main method in the treatment of cervical cancer with hysterectomy or electroendothermy as auxiliary intervention in local recurrences.

The choice between a primary operation or radiotherapy in operable cases is, however, unconditionally dependent on whether or not there is access to a radiotherapeutic clinic with experienced and skilled physicians. It is for the sake of the patients therefore necessary that radiotherapy in cancer be centralized and that adequate instruction and training be imparted by the medical faculties.

Initially, the corpus cancer as well as the cervical cancer were treated with a cylindric radium container placed centrally in the uterine cavity in combination with vaginal radium application as described

above. By this technic, with or without additional external irradiation a cure rate of approximately 45 per cent of the total material and of approximately 50 per cent of the clinically operable cases was attained already in the early 'twenties. From this time on until the early 'thirties these results were not improved in spite of the intensive studies of many radiotherapeutic clinics.

On the assumption that the recurrences in the fundus uteri common in corpus cancer arise from insufficiently irradiated remnants of the tumor HEYMAN in 1929 commenced to elaborate a *method of examination* for the exact localization of the tumor involvement within the uterus and also a *technic of treatment* allowing a more individualized radium application, taking consideration to the size and shape of the uterine cavity.

A differentiated localization of the tumor in uterus and a topographical grouping of the uterine carcinomata have been reached by HEYMAN by a systematically executed *fractional curettage* of the uterine cavity, allowing a minutely localized histological examination of each individual section.

In order to solve the complicated question of distribution of the radium to all portions of the uterine cavity HEYMAN in the years of 1929 to 1939 developed his »*packing method*». The requisite amount of radium is distributed in a considerable number (10—20) of small containers which by means of a special instrumentarium are packed in the uterus until completely filling the cavity. In each case radium is applied in two séances with an interval of three weeks. The treatment time varies with the quantity of radium and the additional filters applied.

In order to prevent vaginal metastases one of the uterine applications is combined with a vaginal application. In addition to the intracavitary radium, roentgen or teleradium irradiation is administered if uterus is fixed or if the tumor has spread to the surroundings of the uterus.

Since 1933 HEYMAN has instituted in cases of corpus cancer also a combined operative and radiological treatment in which radiotherapy plays the primary and main rôle. Surgical interference is resorted to only secondarily in case of failure of the radiotherapy, and as primary treatment in occasional operable cases, such as for instance a corpus cancer complicated with large fibroids or with an ovarian tumor.

After the introduction of the combined method the relative cure rate after at least five years of observation has risen from 44.6 per cent during the period 1914—1933 (158 out of 354 patients treated) to 61.9 during the period 1934—1941 (284 out of 459 patients treated).

55 or 12.2 per cent of the 442 patients alive and without symptoms of the disease have been operated upon after failure of radiotherapy

a ne, the number of cases operated upon being lower in the latter p iod.

In cancer of the corpus the results obtained with the packing method p s operation in case of failure are considerably superior to those ob- t ned by surgery alone.

HEYMAN maintains convincingly that in the corpus cancer also equal o better results will be obtained by primary radiotherapy than by h terectomy plus postoperative irradiation, also involving less risk and l inconvenience to the patient.

HEYMAN's combined packing method in the radium treatment of c pus cancer may be considered as the greatest advance of the recent d ades within the field of radiotherapy in uterine cancer.

Side by side with HEYMAN's principle work, his researches for the fu her development of radiotherapy in cancer of the uterus, stands hi great and important work of *building up an adequate mutual statistical system on the results of radiotherapy in cancer of the uterus* of all ra iotherapeutic clinics working on a scientific basis.

When in 1928 a Sub-Commission of radiotherapists and gynecologists wa set up by the League of Nation's Cancer Commission in order to study the results of radiotherapy in all forms of cancer, it was decided that cancer of the uterine cervix was the most suitable site with which to begin.

The Health Organization of the League of Nations decided to solve the statistical problem by issuing annual reports from selected clinics on their own results of radiotherapy in cancer of the uterine cervix. In order to promote the greatest possible uniformity in the statistical treatment of the material an Advisory Committee was appointed for the purpose of advising the organization on the nature of the observations upon which the annual statistical statements were to be based. The members of this committee were Dr. J. HEYMAN, the Radiumhemmet, Stockholm, Dr. A. LACASSAGNE, The Radium Institute of the University, Paris, and Lt. Col. A. B. SMALLMAN, Ministry of Health, London.

This committee was entrusted with the issuing of the »Annual Reports» and was privileged to invite to collaboration clinics from all over the world whose statistics fulfilled the requirements of the agreed rules and regulations for the presentation of data and for the calculation of results.

JAMES HEYMAN, the leading spirit of the fundamental work, was elected chairman of the Advisory Committee. As editor he dedicated a great part of his time and energy to the organization and the propagation of the »Annual Reports». A modified system for the grouping of the cervix cancer into four stages according to the anatomo-clinical extent of the

growth was elaborated by the Committee and adopted by the Health Organization. In 1938 an Atlas was published illustrating the rules for this stage-grouping in cancer of the cervix uteri, and the Committee contemplated widening the scope of future reports to include analyses of material relative to corpus uteri and the vagina.

The collaboration in these Reports proved to be of great educational value to the clinicians, the comparability of the statistics increasing year by year; the rules and regulations laid down by the Committee have been almost generally adopted. The first volume of the Reports, issued in 1936, contained statements prepared by six collaborators in three countries; the fourth volume, edited in 1940, contains eighteen statements from eight countries. The »Annual Reports» on the results of radiotherapy in uterine cancer have attracted general attention as exemplary for the creation of international statistics in other fields of cancer therapy.

The success of the »Annual Reports» was obvious. Further editions during World War II became out of the question, however, owing to the difficulties in international communication.

As an illustration of the general appreciation of JAMES HEYMAN's contribution to the statistical evaluation of radiotherapy in uterine cancer as editor of the »Annual Reports» I only quote the statement of Dr. HAROLD SWANBERG in this Anniversary Volume that »these reports are the best statistical studies that have been compiled in the study of the end-results of the radiologic treatment of uterine cervical cancer» and that »every gynecologist and radiologist is forever indebted to Professor HEYMAN for the years of labour he devoted to these reports».

Soon after the late war HEYMAN renewed his efforts in re-establishing the collaboration in the statistical work, and in his lecture before the American Medical Association this year he was able to report that — thanks to the support of the British Empire Cancer Campaign, the Donner Foundation in Philadelphia and the Cancer Society of Stockholm — the international collaboration in the »Annual Reports» on the results of radiotherapy in cancer of the uterine cervix has been successfully resumed.

The fundamental driving power in HEYMAN's activity as researcher and physician is his great and unselfish desire to afford the best possible assistance to the suffering patients committed to his charge. Accuracy and unswerving devotion to duty are characteristic to him. His interest in the psychical care of the patients marks his entire activity as a physician. Characteristic to him are also his unremitting striving to improve his results by perfecting his technic of treatment, and his capacity for collaboration in research and in medical treatment. To be his collaborator is to be his friend.

HEYMAN's profound experience and skill within both gynecological surgery and radiotherapy have been of great importance for the development of the gynecological therapy at Radiumhemmet.

His exceptional talents of organization have been greatly called upon. These powers have perhaps best been expressed in the development of the gynecological department at the Radiumhemmet, where he can give account of each and all of his patients since three decades, and where the entire clientele has been so closely observed and described that it in its entirety can be taken as the basis for scientific research.

I have above endeavoured to describe HEYMAN's contribution to the organization of the international statistics of treatment in uterine cancer. Those who attended the International Congress of Radiology in Stockholm in 1928 will not either forget the charming chairman of the organizing committee. His interest for international collaboration is fervent. HEYMAN is a constant participator and an eagerly attended lecturer at the International Congresses of Radiology, where he by his sense of humour, his winning personality and his outstanding knowledge of languages has been in the centre of the gatherings of confrères. Within the gynecological and radiological medical associations in Sweden he has afforded important services and has held several posts of honour.

Not until recent years, when the Professor of Gynecology at the Caroline Institute, AXEL WESTMAN, himself trained in radiotherapy at Radiumhemmet, turned over a part of his courses to HEYMAN for regular instruction in gynecological radiotherapy, he has had the occasion to teach the medical students in this his particular field. But to the multitudes of physicians, however, which through the years have flocked to his clinic not only from Sweden but from the entire world, he has been a never-to-be-forgotten teacher.

Upon HEYMAN have been conferred many scientific honours. He has thus been elected honorary member of several distinguished medical societies in Europe, in India and in America, and has on invitation lectured in medical centres on both sides of the Atlantic. In 1942 the Swedish Medical Association bestowed upon him the »Tage Sjögren Prize», which is awarded to »the Swedish researcher who during the past four years has contributed the most outstanding advances to medical radiology».

The enthusiastic support to this Anniversary Volume also bears witness to the admiration, the gratitude and the friendship which surround JAMES HEYMAN when he at his sixty-fifth anniversary is at the point of leaving that post as chief of the Gynecological Department of the Radiumhemmet which he has held for three decades.

Several of the authors in this Dedication Volume testify that his work has been a stimulus for the research work in gynecological radio-

therapy, and that his methods of treatment have been used to a great extent.

His activities may well be considered to mark an era. Radiotherapy in uterine cancer has in his skilled and experienced management not only equalled the results of surgery, but has even surpassed them, and has afforded new possibilities for the healing or palliation of patients suffering from this disease.

Radiologists and gynecologists of the entire world and multitudes of patients are today united with us in grateful homage to JAMES HEYMAN, in the fervent hope that he for many years may be preserved to medical science and to his friends.

Gösta Forssell.

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OESTROGENS AND TUMOUR GENESIS[1]

by

Bernhard Zondek.

The question whether a correlation exists between the sex hormones and tumour genesis is of utmost clinical as well as of theoretical importance.

A. Animal experiments

A number of investigators have reported that oestrogenic hormone may have a carcinogenic effect in animals. In strains of mice with a high incidence of cancer the rate of mammary cancer can be reduced almost to zero if the ovaries are extirpated at the time of early sexual maturity. (1)

LACASSAGNE (2) first succeeded in inducing the development of mammary cancer in male mice belonging to high tumour strains by repeatedly injecting large quantities of oestrogens over long periods. He showed, moreover, that diethylstilbestrol, physiologically similar but chemically unrelated to the natural oestrogens, was also capable of causing cancer in male mice, thus demonstrating that oestrogens are carcinogenic in mice not because of their chemical configuration but due to their property of physiological stimulation.

It is now well established that the genesis of cancer of the breast in mice involves interaction among at least three factors:

1) Hereditary susceptibility,
2) The presence of the female hormone (oestrogenic hormone).
3) The presence of the so-called mammary tumour inciter.

This last mentioned »milk-factor» is a labile, antigenic, filtrable agent, transmissable from mother to offspring through nursing. Whereas it has not yet been demonstrated that human breast cancer is dependent on a similar set of conditions, still on the basis of our knowledge of breast cancer in mice it has recently been advocated that women from families in which malignant tumours have occurred refrain entirely from nursing their progeny (3, 4).

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Can cancer of the uterus arise as the result of oestrogenic stimulation? Experimental work is less conclusive in this field than with respect to cancer of the breast.

OVERHOLZER and ALLEN (5) observed a very suspicious lesion of the cervix in a castrated *Macacus rhesus* which had received oestrogenic and corpus luteum hormones over a period of 51 days. They submitted the preparation to Dr. JAMES EWING who diagnosed it as the initial stage of a carcinoma. The results of other authors, however, do not support these findings. ENGLE and SMITH (6) treated 4 macacus monkeys for 60 to 170 days with a total of 33,400 to 95,400 I. U. of oestrone without being able to induce any changes of the cervix which would indicate carcinoma. ZUCKERMANN (7) treated monkeys for an even longer period, up to 365 days, with a total of 365,000 I. U. of oestrone. He found erosions of the cervix but no carcinomatous changes. — No confirmed report of endometrial carcinoma in animals subjected to oestrogen treatment has appeared. GREENE (8) has seen metastasizing endometrial tumours in rabbits following a disease described as the counterpart in rabbits of toxaemia of pregnancy in women. He believes that such rabbits fail adequately to inactivate the oestrogen produced by their normal ovaries because of damage to the liver. The endometrium is thus exposed to overstimulation with oestrogen.

LIPSCHÜTZ (9) has shown that treatment of guinea pigs with oestrogens provokes the formation of fibromyomata in their uteri. He states that the atypical metaplastic proliferation of epithelial and connective tissue elicited by the administration of oestrogens to the guinea pig affords characteristic signs of neoplastic growth. This can be counteracted by the administration of progesterone and other related steroids.

B. Observations in man

a) Mamma:

Several cases of cancer of the breast have been reported in women under oestrogen therapy. GARDENER (10) suggested that oestrogens increase the physiological age of tissues, thus rendering them more susceptible to other carcinogenic factors. Although the findings obtained in laboratory animals cannot be applied directly to human beings, it must be the source of a certain amount of anxiety to the clinician to learn that oestrogenic hormone is able to induce carcinoma, even if only rarely and only in animal experiments. ALLABEN (11), AUCHINCLOSS and HAAGENSEN (12), ANSPACH (13), PARSON and MCCALL (14), LOUBEJACK (15) and KELLOGG (16), each reported one such case.

b) Uterus:

NOVAK and YUI (17) conclude that »hyperplasia» (which they define as the condition of the endometrium under continuous oestrogenic stimulation), persisting after the menopause, predisposes to the development of cancer.

HERRELL (18) states that endometrial carcinoma almost always occurs in the presence of a persistently prolifering endometrium resulting from the unopposed action of oestrogens.

HENRY (19) has reported 2 cases in which the prolonged administration of diethylstilbestrol has been followed by the discovery of malignant growths in the uterus. FODGSON and his associates (20), after studying oestrogenic activity in 62 cases of granulosa cell tumours, reported proliferative endometria in 67 %, and concluded that this phenomenon of coexistent ovarian, endometrial and mammary carcinoma in the human being

bea s a marked similarity to the results of experiments on laboratory animals in which oes ogen stimulation appears to be a factor in carcinogenesis.

INGRAHAM, BLACK and RUTLEDGE (21) reported 2 cases of endometrial cancer in wo en with granulosa cell tumours and one in a woman with a thecacell tumour of the ova y. HERTIG (22) stated that 18 to 20 % of his patients with granulosa cell tumours and with thecomas also had associated carcinomas of the endometrium; and G. V. SMITH (23) in a study of 180 ovaries from cases of endometrial cancer found slight to definite evi ence of theca cell activity in 87 %.

On the other hand, JONES and BREWER (24), studying 68 patients with cancer of the end metrium, found only 2 with cystic hyperplasia. These authors doubted the importan e of unopposed oestrogenic stimulation in the causation of endometrial cancer. GEIST and SALMON (25) found no evidence of abnormal proliferation of the endometrium in women who had undergone prolonged treatment with large doses of oestrogens. CROSSEN (26) found the late occurrence of menopause (50 years or over) about four times as frequent in women with endometrial adenocarcinoma as in a healthy group.

FREMONT-SMITH, MEIGS and GRAHAM (27) recently reported the development of cancer of the endometrium after the administration of oestrogens for a period of 8 years. Total dosages of the various oestrogenic preparations used during this 8-year-period were as follows: oestradiolbenzoate or dipropionate, 392 mg (2,352,000 R. U.); oestrone sulfate, 1,085 mg (8,862,000 R. U.); and diethylstilbestrol, 18 mg (450,000 R. U.). The authors state that »the evidence cited does not prove but does strongly suggest that the unopposed action of oestrogens on the breast and endometrium of certain women may result in the development of cancer». After withdrawal of the oestrogen, the vaginal epithelium was found to be atrophic, indicating that the patient was producing little or no oestrogen of her own, and FREMONT-SMITH et al. suggest that this strengthens the supposition that endometrial cancer might not have developed without the administration of extrinsic oestrogens.

C. Our experimental and clinical observations

The following is a summary of our clinical and experimental investigations.

a) Experimental findings.

Prolonged treatment with oestrogenic hormone is able to eliminate the activity of the growth hormone as well as of the gonadotropic hormone in the rat, so that eunuchoid dwarf animals are produced. We have repeatedly reported on these dwarf animals during recent years (28). Although the rats received immense doses of oestrogenic hormone until they died — up to one million international units — no uterine or breast carcinomata occurred in any of our 250 experimental animals, which had been treated for several months, up to half a year. Our Jerusalem strain apparently has no tendency to spontaneous tumour growth, as no spontaneous tumour has so far been observed in 5,000 animals. This may be the reason for our inability to produce uterine carcinoma with oestrogenic hormone. The morphological changes of the uterus which appear after prolonged treatment with oestrogenic hormone are discussed below.

It is noteworthy that various animal species react differently; and that even within the order of rodents varying reactions occur. We find typical changes of the mucosa in the uterus of the rat (29). It is of particular interest that the cylindrical epithelium may be partially or entirely transformed into stratified, keratinized, squamous epithelium, so that the uterus resembles a vagina in oestrus. The glands may also be metaplastically altered. The inexperienced observer may easily confound these glands with carcinomatous growth, whereas the process is actually entirely benign.

A second characteristic phenomenon is an inflammatory process with leucocytic infiltration throughout the entire mucosa, and with leucocytes penetrating into the uterine cavity of the rat. Finally, an infectious suppuration results (pyometra). The muscle is destroyed and the horns are transformed into pus sacs as thick as a finger.

The metaplastic changes were first described by SELYE, THOMSON and COLLIP (30). We have been able fully to corroborate their findings.

Metaplastic changes were also found in the uteri of treated mice, particularly when the injections were started in very young animals (31). In older animals receiving large amounts of oestrogens, metaplasia occurred less regularly and was associated with cystic glandular hyperplasia or with septic inflammation. In all these cases the stroma had undergone fibrosis or hyalinization. Epithelial metaplasia did not occur in uterine horns ligated near the cervix or in uterine horns grafted subcutaneously, although these persisted in a cystic state throughout the period of treatment (32).

Pyometra and death due to peritoneal involvement frequently occurred after a few weeks. Bacterial invasion was apparently responsible for the suppurative uterine inflammation, as transplanted uteri did not show pyometra (33).

The uterus of the rabbit reacts quite differently to prolonged administration of oestrogenic hormone (34), which has never led to the above described metaplasia in the rabbit. In this animal we must distinguish between the proliferative and the destructive process. To begin with, the reaction of the uterine mucosa consists of glandular cystic hyperplasia. The destructive process follows. If a rabbit is inoculated with oestradiolbenzoate for several weeks, thrombosis of the uterine blood vessels occurs. Infarct-like necrosis of the uterine wall then follows, accompanied by secondary aseptic suppuration of the uterine horns. Our findings have been corroborated by GARDNER (35).

This process can be considerably accelerated by introducing a pellet containing 10 mg. of oestrone into one uterine horn (36). After some days haemorrhage as well as necrosis may be observed in the uterus. In no instance, however, were carcinomatous changes found.

In the rabbit, therefore, small doses of oestrogenic hormone further th development of the mucosa, while larger doses destroy the uterus. W ereas epithelial changes are the main characteristics in the rat, in th rabbit thrombosis is the most striking event. The mouse occupies an in rmediate position. In all cases, however, the uterus is eventually de royed by suppuration, which runs its course aseptically in the rabbit ar mouse, while it is infectious in the rat.

ALLEN's work (37) with castrated monkeys has shown that oestrogens can produce enc nous proliferative growth of the vaginal epithelium with an increase in the number of owing bulbs along the basement membrane, and with many mitotic figures among the ells. Epithelial metaplasia of the uterine fundus has not been described in monkeys. Aft a period of epithelial proliferation, largely completed soon after the start of injection, the cells of the lumen and the glands of the fundus become laden with glycogen (38) and persist in such a state for long periods (39).

We learn from the described experiments that different species of animals react differently to the same hormonal stimulus. When experimental production of carcinoma comes into question, we should, therefore, hesitate to transfer conclusions from one species of animals to another, especially to human beings.

b) Investigation in man.

What are the conditions in human beings? — As we were able to demonstrate in 1935 (40), the administration of oestrogenic hormone interferes with the normal menstrual cycle. If doses of over 60,000 I. U. are injected into a normally menstruating woman during the postmenstrual or intermenstrual stage, the subsequent menstrual period is delayed by 7 to 70 days. In this way artificial amenorrhoea is produced. We had the opportunity of examining specimens of the uterine mucosa and corpora lutea during operations, and we noted the following facts. Large doses of oestrogenic hormone prevent corpus-luteum formation, or cause its rapid degeneration, so that only insufficient or negligible amounts of progesterone are produced. The progestational transformation of the uterine mucosa does not take place, and the second generative phase is thus suppressed. From the fact that we found decreased FSH excretion in these cases, we concluded that the oestrogenic hormone acts primarily on the anterior pituitary, preventing the secretion of the gonadotropic hormone. In addition to this central inhibitory effect, oestrogens stimulate the uterine mucosa locally and can thus induce enormous proliferation, also of a cystic nature, even with the formation of polyps.

re there also carcinomatous changes? In 1940, we described our own cases treated with large doses of oestrogenic hormone (41). Although we have used oestrogenic hormone therapeutically for 20 years, we

have never encountered any changes of the uterus in which we could implicate the carcinogenic action of the hormone. We treated amenorrhoic women, who repeatedly received 200,000 to 400,000 I. U,. or even 800,000 I. U. of oestrone or oestradiolbenzoate, but no clinical changes of the uterus indicative of carcinoma ever appeared in these patients. In two cases anatomical examinations have been carried out:

1. Patient N., aged 23, sterile. Her menstruation had been regular and had lasted for 4 to 5 days. A diagnostic curettage performed before menstruation showed that the mucous membrane was in the premenstrual stage with normal glycogen content.

From the 4th to the 27th day of the cycle the patient received 50,000 I. U. of oestradiolbenzoate daily, *i. e.*, a total dosage of 1,200,000 I. U. On the 28th day of the cycle, a biopsy of the cervix and a curettage were performed. The findings were as follows:

The portio was perfectly smooth, and there were no erosions. Glands were strikingly abundant in the cervical mucosa. The lumina of the glands were very wide and in certain portions were so cystically dilated that under low power some of the glands occupied an entire microscopic field. Some of these glands were lined with tall, columnar epithelium with flattened nuclei (goblet cells), which formed papillae at certain points. In the lumina of the glands, mucous-like plugs without cellular elements and, very rarely, desquamated cells were seen.

It may be assumed that the hormonal stimulus brought about the increase of the glands.

In places where there were no glands we observed a large number of thick-walled blood vessels with hypertrophied media, and numerous dilated veins. The uterine mucosa was typical of the intermenstruum. It corresponded to the 12th day rather than to the 28th day of the menstrual cycle. BEST's stain for glycogen was negative. Quantitative examination of the glycogen content of the uterine mucosa revealed 0.05 %, whereas the physiological content on the 28th day of the cycle is about 0.28 to 0.66 %. (42).

These two observations demonstrate that the administration of 1,200,000 I. U. of oestradiolbenzoate, *i. e.* three or four times the dose used in treating amenorrhoea, inhibits the development of the uterine mucosa in women, and moreover, increases the number of mucous glands in the cervix, but does not bring about any suspicious changes.

3. The following is the description of a case which received 0.6 g. of oestradiolbenzoate (6,000,000 I. U.) over a period of 60 days. The patient was a young woman, aged 26, in whom both mammae had been removed because of a bilateral mammary carcinoma. On admission, local recurrences were noted, pleural metastases (pleural exudate) and vertebral and cutaneous metastases (lymphangitis carcinomatosa). In addition metastases were found at autopsy in the liver and ovary. In this desperate case we attempted to inhibit the growth of the carcinoma by very large doses of oestrogenic hormone. We were induced to attempt this treatment for the following reasons: 1) Large doses of hormone inhibit the release of the gonadotropic hormone from the anterior pituitary into the blood stream so that the ovarian function ceases. As is well known, castration favourably influences mammary carcinoma, and we tried to attain this end in a similar manner by »hormonal castration». 2) It has been reported in the literature (43) that the growth hormone of the anterior pituitary hastens tumour growth. If rats, which have been inoculated with Jensen-carcinoma are hypophysectomized, the tumours do not grow. If Evans' growth hormone is now administered to the animals, tumour growth continues.

Large doses of oestrogenic hormone are able to produce dwarfism by inhibiting the release of the growth hormone of the anterior pituitary into the blood stream. We attempted to inhibit the growth of the breast carcinoma by eliminating the growth hormone with large doses of oestrogens. In such an advanced case we were unable to observe any perceptible influence on the mamma-carcinoma and its metastases. It may be that our doses (10 mg. of oestradiolbenzoate daily during the 60-day period of treatment) were still too small. Our case represents the first recorded attempt to inhibit the growth of carcinoma by continuous treatment with oestrogens.

These experiments were more successfully continued by others. During my stay in Boston 1947, Dr. IRA NATHANSON (General Massachusetts Hospital) informed me about his successful cases of inoperable mamma-carcinoma continuously treated with stilboestrol for several months. Particularly noteworthy are the results in cases of prostata-carcinoma, especially with regard to its metastases in the spinal column, as described by HUGGINS (44). These results are too well known for a detailed description to be necessary. There can be no doubt that the success of oestrogen treatment in cases of prostata-carcinoma depends on inhibition of the gonadotropic function of the anterior lobe, and on a secondary atrophy of the testicles, *i. e.* a hormonal castration. This is the more evident since remarkable improvement after surgical castration was already reported some decades ago in such cases. Oestrogen treatment is of considerable value in prostatic cancer, but its beneficial effect has not yet been established for a long enough period. Since the first report of HUGGINS et al. (44) numerous confirmations have been published by KEARNS (45), KAHLE et al. (46), MARQUARDT and FLAHERTY (47), HERBST (48), CHUTE and WILLETS (49), HECKEL and KRETSCHMER (50), and SCHENKEN et al. (51). It is still too early to evaluate the significance of this important method of treatment of a hitherto intractable disease.

Returning to our case of mammary carcinoma treated with 0.6 gram of oestradiolbenzoate, we observed the inhibition of menstruation apart from some slight bleeding, and atrophy of the ovaries; whereas the local stimulus of the oestrogenic hormone led to an enormous glandular cystic hyperplasia of the uterine mucosa and to a papillary erosion of the portio. The anatomical findings of the genital organs and other endocrine glands are as follows:

Anatomical findings. Uterus: On gross examination the vagina appeared normal and the external os of the uterus was round. A large, circular, chiefly papillary erosion was observed in the uterine portio. The mucous membrane of the cervical canal was bright red. The plicae palmatae were particularly marked. Above the internal uterine os there was a pale zone 0.5 cm. wide (corresponding to the lower uterine segment, »Dehnungszone«). This pale zone contrasted strikingly with the dark red mucous membrane of the corpus uteri. The latter had a very unusual appearance. There were netlike whitish formations on the surface. On submerging the specimen in water a great number of floating masses, looking like fine polypi, appeared.

Microscopic findings. At the level of the internal orifice of the oviduct, the glands were slightly enlarged and not tortuous. The rest of the mucous membrane of the corpus, however, showed markedly distended glands which were inflated in a balloon-like fashion, protruded into the lumen and were frequently torn. These were the areas that corresponded to the polyp-like masses seen on gross examination. That the tears were spontaneous was proved by the fact that even the glands of the deeper layers of the mucous membrane occasionally were similarly ruptured. The epithelium of the glands was cylindrical, although in some places it was flattened in an endothelial manner, and such areas were found in both the normal and the distended glands. The lumina of the glands were empty for the most part, but occasionally were found to contain a considerable number of erythrocytes. The mucous membrane of the corpus was strikingly hyperaemic, with markedly engorged, thin walled blood vessels, lined by endothelium alone, and without adventitis. In some portions no endothelial nuclei were present and the wall was demarcated merely by a delicate line of plasma. Rather active diapedesis had apparently taken place particularly in this area, as erythrocytes could be found in the adjacent stroma in areas where the endothelium had abundant nuclei. There were slight interstitial haemorrhages, but a break in the continuity of the vessel walls was nowhere to be detected. The haemorrhage which had occurred on the day of death could not have been due to the rupture of the superficial capillaries, but was probably due to diapedesis and to the exudation of blood from the ruptured glands.

Thus the uterine mucosa presented a peculiar picture of glandular cystic hyperplasia. The glands, which were ruptured in many places, projected in a balloon-like fashion into the lumen. There was a considerable degree of hyperaemia and haemorrhage. Towards the lower uterine segment (»Dehnungszone«), the mucous membrane suddenly became quite thin and the glands were no longer either inflated or torn. The blood vessels were narrow and contained no erythrocytes. Thus, the thin anaemic mucosa of this zone contrasted with the thick hyperaemic mucosa of the corpus.

In the cervix the openings and the lumina of all the glands were distended. The lining epithelium was tall and columnar, and there was no hyperaemia.

The cervical mucous membrane extended over the vaginal surface of the uterine portio. Bordering on the squamous epithelium (the remainder of the vaginal surface of portio), the stroma was infiltrated with lymphocytes and plasma cells, and the histological picture was that of a common papillary erosion of the portio. The rather anaemic mucous membrane of the cervix became hyperaemic at the area of erosion. Beginning near the site of erosion, there were within the squamous epithelium of the portio (remainder of the vaginal epithelium of the portio) some scattered ridges of epithelium, containing dilated blood vessels and extending into the stroma. Towards the vagina, small epithelial buds extended into the depth of the stroma, though these buds were fairly distant from each other. Hyperaemia was observed in this area, and the stroma was sparsely infiltrated with round cells. Some of the epithelial projections were pedunculated, and it appeared that some of them were separated from their origin. At no point was there any evidence of carcinoma.

Ovary: No primitive follicles, no ripening follicles, no fresh corpus luteum were found, but there numerous corpora albicantia with remainders of lutein cells were observed. In both ovaries there occurred extremely small carcinomatous metastases of the primary cancer of the breast.

Pituitary gland: The gland weighed 710 mg. (The average weight, according to Erdheim-Stumme, for the age group of 21 to 30 for nullipara, is 595 mg.) The gland was fixed in Orth's fluid and imbedded in paraffin. In cross sections, through the anterior lobe a discrete pale nodular area delineated by a delicate reddish line, was seen with the naked eye. Exact measurement revealed that this area occupied half of the anterior lobe.

Microscopic findings: The posterior lobe failed to show any considerable deviation fr[om] the normal. Anterior lobe: The lower and anterior part were almost normal as to ce[llu]lar structure, although a preponderance of eosinophilic cells was noted at some points. T[he] circular area which we had already observed on gross examination in the upper, po[ste]rior zone appeared to consist almost exclusively of eosinophilic cells (Azan-stain, m[odi]fied according to PETERSON). This area was limited anteriorly by a wide band of fib[rou]s tissue with abundant blood vessels. In the other portions, the eosinophilic nodule wa[s] defined by a sudden change of the cellular character without any limitation by a fib[rou]s capsule.

Anatomical diagnosis: Circumscribed hyperplasia (according to another terminology »ad[e]noma») of the eosinophilic cells.

The other ductless glands, thyroid, parathyroid, adrenals and pancreas were normal.

The striking enlargement of the cervical glands observed in all three cas[es] was probably due to the hormonal treatment.

In the first two cases (28 days' treatment with 1,400,000 I. U. oestradiolbenzoate), the portio showed no erosion. In the third case (6,000,000 I. U. during 60 days), an extensive papillary erosion of the portio developed during the period of treatment. Within the area of the erosion, however, no carcinomatous changes could be found. Even after so protracted a treatment with large doses of hormone, we found no carcinomatous changes in the uterus in spite of the fact that the patient was suffering from a progressive cancer. The continuous administration of large doses of hormone cannot, however, be considered to be entirely harmless, since an extensive erosion of the portio developed during the period of treatment. Care should be taken if an erosion is already present, previous to treatment; for it is theoretically conceivable, that the chronic hormonal stimulus might give rise to the development of a malignant formation at the site of a pre-existent erosion. For this reason it is necessary not to administer hormonal treatment continuously, but to allow intervals without treatment to intervene. Treatment with oestrogenic hormone should not, as sometimes happens, be continued uninterruptedly for months.

Pituitary adenoma: The anterior pituitary, in the third case, contained a large eosinophilic area occupying half of the entire anterior lobe. Such formations are called pituitary adenomas in the current literature. In our case the fibrous border was only partially complete. We should designate such formations as »circumscribed hyperplasia». The question arose, whether the large eosinophilic »adenoma» observed by us was a consequence of the chronic treatment with oestrogenic hormone, or whether it was a coincidental finding.

COSTELLO (52) systematically examined 1,000 hypophyseal glands from the autopsy material of the Mayo Clinic in Rochester, Minn. and found a total of 265 adenomas in 225 of these glands. These were classified as follows: chromophobic, 140 (82.8 %); eosinophilic, 20 (7.[5] %); and basophilic, 72 (27.2 %). Among 1,000 hypophyseal glands there were no

more than 20 eosinophilic adenomas (2 %). Eosinophilic adenomata occur much less frequently than basophilic ones, although in the human hypophysis eosinophilic cells (37 %) are much more frequently found than basophilic ones (11 %), as reported by RASMUSSEN (53). CLOSE (54) observed that the incidence of pituitary adenoma in a series of routine post mortem examinations was approximately 10 % (280 cases), but that it was as high as 44 % in cases with associated carcinoma in other glands. CLOSE found no adenomas of the pituitary in two cases of mammary carcinoma and in one case of ovarian carcinoma. This fact is important for the evaluation of our case. In the vast majority of cases the adenomas consisted of chromophobic cells. In only two cases out of 39 were eosinophilic adenomas described. As shown by the investigations of KARLEFORS, BERBLINGER and MUTH, if carcinoma induces any changes at all, it brings about an increase in the number of the chromophobic cells, with their occasional transformation into pregnancy cells. Spontaneously occurring pituitary adenomas need not give rise to clinical symptoms, and COSTELLO therefore calls them »subclinical adenomas».

It can, therefore, scarcely be proved with certainty that the anatomical findings in the anterior pituitary are merely accidental. The following considerations lead us to believe that in our case the eosinophilic »adenoma» was a consequence of the chronic administration of hormones: a) An eosinophilic adenoma is very rarely encountered, b) the case we recorded was a very large adenoma occupying half of the entire anterior lobe, and such large eosinophilic adenomas very rarely occur spontaneously.

In the rat prolonged treatment with oestrogenic hormone — as mentioned below — led to chromophobic hyperplasia of the anterior pituitary lobe (55). In view of the fact that even animals of the same order, *e. g.* various species of rodents, differ greatly with respect to their reaction to hormone treatment, it is not surprising that the cellular reaction of the anterior pituitary to chronic treatment with oestrogens is not the same in humans as in laboratory animals. Though treatment with oestrogenic hormone in our human case inhibited the release of the growth hormone, the number of eosinophilic cells in the pituitary gland increased considerably. The fact that the other endocrine glands, particularly the thyroid, were in no way affected was of great interest.

Chronic administration of oestrogens to rats induces inhibition of the growth- and gonadotropic-hormone secretions, thus producing eunuchoid dwarf rats. Whereas the bones and all the viscera are smaller then normal and the sexual organs are completely atrophic, there is one exception, the anterior pituitary gland being enlarged. During the early stages of treatment the enlargement progresses quite gradually, but after a few months' treatment there are enormous changes in its size.

It has been discovered simultaneously in three different laboratories working independently of each other that prolonged treatment with oestrogenic hormone is capable of giving rise to hypophyseal tumors:

. CRAMER and HORNING in London (56) reported on hypophyseal tumours in mice on February 1, 1936. They painted the skin of 12 mice twice weekly with a 0.01 % chloroform solution of oestrone. Only one pituitary gland remained normal on gross examination while 8 were macroscopically enlarged without alteration of the general shape and without gross pathological lesions in the gland. Three exhibited definite adenomatous tumours, nodular, round, deeply congested and haemorrhagic.

. In January, 1936 we observed, in Jerusalem, the first hypophyseal tumour and reported this finding on April 4, 1936 (55).

. On the very same day MCEUEN, SELYE and COLLIP of Montreal described similar findings (57). They reported that they had produced enlargement of the pituitary gland as well as several large cavernous adenomas by treating rats with oestrone for several months.

Later BURROWS (58) in London (1937) reported that, among 679 mice treated percutaneously with oestrogenic hormone for 483 days, only one case of hypophyseal tumour was found. We, however, succeeded almost regularly in inducing these tumours in rats by the subcutaneous and percutaneous application of oestrogenic hormone over a period of 7 to 9 months.

It is the duration of treatment rather than the amount of hormone administered, that is of utmost importance. After eight months' treatment, tumours developed in 80 % of our cases. They were equally regularly obtained by rubbing a benzolic hormone solution into the skin.

The same amount of gonadotropic hormone occurred in the enlarged glands of the dwarf animals as in those of the controls. This seems to be important since it demonstrates that it is not the production of gonadotropic hormone but rather its delivery into the blood stream that is inhibited.

The pituitary tumours are always fatal and give rise to symptoms associated with intracranial pressure. The animals move slowly, eat poorly, are ataxic and show loss of orientation. In some there is a fine tremor of the entire body, which is intensified by handling. Four animals turned continuously to the right, or rolled around their axes. The most characteristic sign, however, is a fall in the temperature, the mechanism of which cannot be explained with certainty, but is probably to be ascribed to pressure on the third ventricle. In any event, it indicates the formation of a tumour. It is not due to hypoglycaemia, since the blood-sugar was found to be within normal limits.

Ophthalmological examination of the fundus revealed a marked contraction of the vessels, which did not seem to depend on the presence of a tumour, since it was seen in one case where the pituitary was small. It would seem that this contraction of the vessels is the result of prolonged treatment with oestrogenic hormone.

Dr. ARTHUR WEIL of the Northwestern University, Chicago, was kind enough to examine the pituitaries of our experimental animals (59). The results were, in the main, similar to those obtained by WOLFFE (60). The chromophobic cells were no longer converted into chromophilic ones,

thereby relatively increasing in number. Eventually the large pituitary glands came to consist chiefly of chromophobic cells. The eosinophilic cells had undergone degranulation. The Golgi apparatus of all three cell types was enlarged. There were extensive haemorrhages in the anterior lobe and in the interlobular cleft. The animals died with symptoms of intracranial pressure, probably as a result of pituitary apoplexy. They succumbed to their tumours, although anatomically these formations were entirely benign. We attempted to transfer these tumours to rats, but were unsuccessful. In order to provide better conditions for their growth, we grew part of the tumour material in plasma culture media, and observed that the pituitary tissue grew well. After some time we transplanted the tissue together with the plasma to rats. This procedure also proved unsuccessful.

In further experiments we studied the question whether simultaneous treatment with carcinogenic substances and sex hormones would accelerate tumour growth in rats. Seven weeks' painting of the skin with 1 % benzpyrene solution in benzol produced cutaneous papillomas and carcinomas. The simultaneous administration of oestrogenic hormone did not accelerate this process.

Effect of oestrogen pellets

The effect of oestrogen pellets implanted in women has been studied by us over a period of 4 years. No case of tumour formation has so far been encountered. Recently we reported on an interesting experiment in a rabbit (61). As late as 16 months after the implantation of a 10 mg. pellet of oestrone, an extraordinary combination of changes was observed, viz., well proportioned giant growth, with a body weight reaching 3,900 g., as against only 2,900 g. in the control; enormously swollen breast glands, milk production equal to that in a lactating rabbit after parturition, and ovaries weighing 1.1 g (as compared with 0.2 g. in the control) consisting of a solid mass of lutein tissue entirely lacking in primordial or mature follicles. Marked alterations were also found in the other sexual organs, but these could be attributed to local and direct effects of the implanted oestrogen. Thus, particularly large, *benign, tumour-like polyps were found at the portio uteri; excessive proliferation with polyp formation was noted in the vaginal and uterine mucosa;* and degenerative changes of a type already described (62), especially hyperaemia, bleeding and infarct-like necrosis of the myometrium, were seen in the uterus. Summarizing, it was possible to suggest that uninterrupted stimulation of the anterior pituitary with oestrone (through continuous resorption from the implanted pellet) is able to induce hypersecretion of the growth hormone, the gonadotropic hormone (luteinizing factor) and the lactogenic

hormone. Regular daily resorption of about 0.018 mg = 180 I. U. of oestrogen was necessary to obtain this effect. No malignant tumour formation was observed.

Vitamin deficiency, hyperoestrinism and tumour formation

In 1934 (63) we were able to demonstrate that the liver inactivates oestrogens in the body, probably by means of a special liver enzyme (estrinase). While further investigation is still in progress to clarify the exact relation of the liver to oestrogen metabolism, the BISKINDS (64) have found that the liver loses its ability to inactivate oestrogen in B complex deficiency in female rats, and that this can be controlled at will by the administration of vitamin B complex or its restoration to the diet.

In an attempt to correlate B complex deficiency, decreased liver function and, consequently, high oestrogen blood titer, AYRE and BAULD (65) studied two series of 150 and 20 cases of proved cancer of the corpus uteri.

In over 66 % of the first series of 150 proved cases of intrauterine cancer evidence of abnormally high endogenous oestrogenic activity was obtained by the vaginal smear test. In the supplemental series of 20 patients 90 % were found to have a low thiamine excretion with an abnormally high oestrogen level. Twenty percent of this group also exhibited deficient excretion of riboflavin.

AYRE and BAULD state that fixed habits of diet and dietary errors over long periods of time may produce unrecognized chronic deficiencies. These may act on the liver in man as in animals and thus allow the accumulation of oestrogens in the body, and consequently permit the hormones to act as a growth stimulant of oestrogen-susceptible tissues such as the pelvic organs and possibly also the glands of the breast. AYRE and BAULD conclude that there appears to be excellent circumstantial evidence that nutritional deficiency may be a primary factor in the production of uterine cancer, and that the recognition of the possibly dangerous precancerous linkage of low thiamine and abnormally high oestrogen may lead to dietary correction and the possible prevention of cancer.

In experimental investigations we have found that rats with a vitamin B-free diet, even those which, in consequence of the vitamin deficiency were in very poor condition, were able to inactivate the injected oestrone exactly to the same extent as control animals. It is, therefore, doubtful whether vitamin B deficiency has any relation at all to the inactivation of oestrone *in vivo*. During the war the usual disturbances following vitamin B deficiency occurred much more frequently in Palestine than before (67). Nevertheless, the incidence of corpus carcinoma did not increase. Thus, on the basis of these clinical observations, as well, we are not at all sure that any relationship exists between B deficiency,

defective inactivation of oestrogenic hormone, increased oestrogen ti er and the genesis of corpus carcinoma.

Conclusions

The natural as well as the synthetic oestrogenic hormones (stilbest ol etc.) have a twofold effect: a) primarily — stimulation of the growth of the genital organs, b) secondarily — inhibition of the gonadotropic fu ic-tion of the anterior pituitary lobe when administered in large doses, thus leading to atrophy of the gonads.

By reason of its stimulating effect, oestrogenic hormone is capable of inducing benign tumours of the female organs in laboratory animals and in man. In our experiments we produced polyp-like tumours in the vagina of rats as well as papillary polyps of the vagina and cervix in rabbits. By the administration of enormous doses, we produced benign chromophobic tumours of the anterior pituitary lobe in rats, causing the death of the animals as a result of intracranial pressure.

Conclusions based on animal experiments should be applied to human beings with extreme caution, since even various species of laboratory animals react quite differently to oestrogenic hormone. The metaplastic transformations of the uterine mucosa into layers of stratified, squamous, keratinized epithelium, which could be obtained in rats, did not occur in similarly treated rabbits. The uterus of rabbits reacts quite differently, with thrombosis, infarction of the uterine muscles, and with secondary necrosis. Similarly, oestrogen did not induce metaplastic transformation of the uterine mucosa of the monkey (ALLEN). LIPSCHÜTZ was able to produce myoma-like tumours with oestrogenic hormone, but he succeeded particularly with guinea pigs, and not with other animals.

In our rat strain, in which we have never observed a spontaneous tumour, we were unable to produce a malignant tumour, though hundreds of animals were treated with enormous doses of oestrogens over a period of months, until the eunuchoid dwarf animals perished as a result of the intracranial pressure due to their hypophyseal tumours.

By the administration of very large doses of oestrogen for long periods, we produced in women a papillary erosion of the cervix, striking abundance of the cervical glands, as well as an enormous glandular cystic hyperplasia of the uterine mucosa, appearing in the form of fine polyps, with ruptured, balloon-like glands projecting into the lumen of the cavum uteri.

The important question is whether it is possible to induce cancer by the administration of oestrogens. There can be no doubt that this can occur in rodents, as described above, especially in strains with heredi ary susceptibility. It is, however, considerably more difficult to proc uce

cancer with oestrogens in the monkey, and only isolated positive cases are reported by OVERHOLSER and ALLEN, whereas other authors obtained negative results (ENGLE & SMITH, ZUCKERMANN). Some cases have been described in which women under oestrogen therapy are said to have developed mamma carcinoma, but it is always difficult to decide in such isolated cases whether this occurred post hoc or propter hoc. We ourselves never observed the inducing of any malignant tumour during 20 years of clinical experience with oestrogenic hormone. If oestrogens were really capable of producing malignant tumours, mamma- and uterus-carcinoma would have increased considerably during the past two decades, because a great many women have been treated (some unnecessarily) with oestrogens for months, and even for years. In my opinion, the fear that oestrogenic hormone produces cancer in human beings is highly exaggerated. Oestrogenic hormone is a harmless drug, although the limits of its dosage must, of course, be strictly adhered to, as with every other drug. Insulin, thyroidin and pitocin, for example, which are numbered among our most useful therapeutics, may do harm if administered in exceedingly high doses. Should conclusions gathered by oestrogen treatment of laboratory animals be transferred to treatment of man (although — as is shown above — there is no justification for such a course) the following precautionary measures should be taken:

1) In the climacteric, when there is an increased tendency to malignant tumours of the breast and the genital organs, oestrogenic hormone should be administered only in small doses, and not continuously, but with intervals of several days between periods of 1 to 2 weeks of treatment, so that the liver may be able to inactivate the surplus hormone.
2) Oestrogen therapy in women with portio erosion, and mastitis cystica, should be avoided as far as possible.
3) The same is recommended in cases of women from families with hereditary susceptibility.

In my opinion, it is so far not proved that these precautionary measures (1—3) are necessary. Since the results of animal experiments cannot, however, be denied, we think it better to adopt these restrictions in order to be absolutely certain that oestrogenic hormone, one of our most important therapeutics, will bring only help and never harm. The fact that oestrogens have been employed during the past few years as a remedy in certain kinds of carcinoma (mamma and prostata) is a further argument in favour of the view that the fear of the carcinogenic effect of oestrogen in man has been highly exaggerated.

SUMMARY

In the literature there are some investigations reporting on benign tumours arizing in the genital organs of both women and animals after administration of oestrogenic hormone. From the therapeutical point of view it is essential to know whether oestrogen is carcinogenic. In rodents and occasionally in monkeys carcinogenic effect of oestrogen has been stated. In the human subject however no convincing results could be demonstrated. Clinical use of oestrogenic hormone during 20 years has not produced a single case of cancer. Should the cancerigenic effect be actual, the number of cancers both of the uterus and of the breast would certainly have been greatly increasing. As a matter of fact a large number of women undergo oestrogen treatment for many months, and years.

The fact that oestrogen is used for treatment of cancer (prostate, breast) contradicts the carcinogenic action of oestrone.

When at all damages may be caused it is by continual and very prolonged administration of oestrone.

Administration of oestrogenic hormone is advised to be carried out with greater caution when the patients are suffering from a cystic mastitis or a cervical erosion, as well as in women belonging to cancerous families.

ZUSAMMENFASSUNG

Nach Übersicht der Literatur werden eigene Untersuchungen mitgeteilt über durch œstrogene Hormone erzeugte benigne Tumoren an den weiblichen Genitalorganen bei Mensch und Tier. Es wird die für die Therapie wichtige Frage diskutiert, ob œstrogenes Hormon Carcinom erzeugen kann. Wohl ist dies bei Nagetieren und in vereinzelten Fällen auch beim Affen berichtet worden, während die Befunde am Menschen nicht überzeugend sind. Bei 20-jährigem klinischen Gebrauch von œstrogenen Hormonen ist nie ein Fall von Carcinom beobachtet worden. Wäre dies der Fall, so hätte die Zahl der Uterus- und Mammacarcinome enorm zunehmen müssen, da soviele Frauen — häufig ohne Indikation — monate- oder jahrelang mit œstrogenem Hormon behandelt werden. Die Tatsache, dass œstrogenes Hormon sogar als Therapeuticum bei Cancer (Prostata, Mamma) benutzt wird, spricht gegen die carcinogene Wirkung des Oestrons. Wenn überhaupt, so kann œstrogenes Hormon schädlich wirken, nur wenn es länge Zeit kontinuierlich genommen wird. Bei Frauen mit Mastitis cystica und bei bestehender Portioerosion sowie bei Patienten, die aus Ca-belasteten Familien stammen, ist es ratsam mit der Anwendung des Hormons vorsichtig zu sein.

RÉSUMÉ

Dans la littérature on trouve quelques recherches où on a pu produire par l'hormone œstrogène des tumeurs bénignes des organs génitaux de la femme et des animaux. La question importante au point de vue thérapeutique est de savoir si l'hormone œestrogène est carcinogène. Chez les rongeurs et dans quelque cas chez les singes l'effet carcinogène de l'œstrone a été rapporté. Ces résultats n'ont pas été cependant convainquants chez l'homme: pendant 20 ans d'usage clinique de l'hormone œstrogène nous n'avons pas observé un seul cas de cancer. Si l'effet cancerogène était vrai le nombre de cancer de l'uterus et du sein aurait certainement beaucoup augmenté, parce que un grand nombre de femmes sont traités pendant des mois et des années par l'œstrone.

Le fait que l'on s'en serve de l'œstrone pour le traitement du cancer (Prostate, sein), constitue également une preuve contre l'action carcinogène de l'œstrone.

Eventuellement l'œstrone pourrait être nuisible si on l'administre d'une façon co tinuelle pendant très longtemps.

Chez les femmes qui souffrent d'une mastite cystique ou érosion cervicale ainsi qu chez les femmes provenant des familles cancéreuses, il faut être prudent avec l'adm istration de cette hormone.

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THE CENTRALISATION OF CANCER TREATMENT[1]

by

Ralston Paterson

The Radiumhemmet, on the staff of which Professor HEYMAN has so long been an illustrious member, has contributed to the improvement of cancer treatment, not only in the scientific field but also through its demonstration of the advantages of centralisation in the radiotherapeutic treatment of cancer. It seemed to me, therefore, an appropriate contribution to this dedication volume to consider »the case for centralisation». I do so, however, with as background, the pattern of medicine as it exists in Great Britain and in most of the countries of the British Commonwealth of Nations.

I believe that even without new discovery, centralisation of the treatment of cancer in itself does lead to better results than those which are achieved within the present pattern of British medicine. The medical mind is instinctively averse to extreme centralisation — often, indeed, with some justification — so we have first of all to examine why such centralisation is necessary and then see in what respects it has something new to offer.

The first of the realities of the present situation can best be appreciated by a glance at vital statistics of any country in the world. In none are the registered cancer deaths diminishing. In countries or states, taken as *whole units*, the numbers cured must therefore be too small a fraction of the total number to affect vital statistics. There is no doubt that in selected areas excellent work is being done in the treatment of certain types of cancer. Yet great tracts of every country, even in England with its small distances, are still scarcely touched by modern knowledge in this field.

The second of the realities is that although cancer incidence is not increasing in the sense that an epidemic disease increases, yet it is be-

[1] Submitted for publication, June 6, 1947.

coming an increasing menace because of the steadily rising average age of the population. In his report on Social Security in England, Sir WILLIAM BEVERIDGE, quotes figures to show that the percentage of the population of England over 60 (women)—65 (men) will rise from its present 12 % to no less than 21 % in 1971. With this rise the incidence of cancer on the population as a whole will equally rise till it becomes the most common cause of death. What is true of England now will in due course equally hold for all countries as the natural result of modern public health and its increased expectation of life.

The third reality is the one which ought to be the antidote to the first two if only we went about things properly. Enough is known now were existing knowledge employed more thoroughly and more promptly, greatly to improve the probabilities of cure in a number of types of cancer. Admittedly, enough is not yet known to influence the outcome in all of the cancers but a good beginning has been made. The chief of these curable cancers are the accessible growths — those of the breast, mouth, skin, uterus and rectum. By re-organisation alone and by making that which is at present available to a fortunate few available to all, the chance of survival of patients suffering from these and other types of cancer could be greatly improved. In the treatment of those cancers at present less curable a steady advance would also result from the concentrated study made possible by the segregation of large groups of cases to single units for investigation and for research. That this is not mere theory has been clearly demonstrated by the results achieved where there has been a high degree of centralisation into units specialised to this one purpose — units for which the Radiumhemmet, the Fondation Curie, and the New York Memorial Hospital, paved the way. These must now be regarded as having been pilot institutions, and the next step is to ensure that everywhere, and accessible to all, there are similar units. These must be big enough to attract so many cases of *each* of the treatable cancers that the staff becomes extensively experienced both in the diagnosis of cancer and in mastery of the technique of its treatment.

To provide such units on an adequate scale usually becomes a problem for State action, and a good example has been set by Sweden. In England a start has been made by passing an Act of Parliament, known as the Cancer Act, although its implementation has been sadly delayed by the War. Many of the States of the U. S. A., the Provinces of Canada, and the States of the Australian Commonwealth are also planning in this field.

Outside Sweden such a proposal still entails a very big change in outlook towards this disease, and in organisation for its treatment. It will therefore need very full and genuine co-operation between govern-

m nt authorities and the medical profession of planning areas. It will re uire the smaller towns to forego their usual desire to do things for th mselves in favour of collaboration with the big city of which they ar sometimes jealous. Small areas, or individual hospitals, cannot provide ad quate cancer services for themselves.

There is a second reason for such centralisation — a reason so obvic is that it is usually presented as the main argument. It is the need to arry extensive and varied supplies of radium containers and to own suf icient modern Roentgen plants. These things are all important but sho ld not blind us to the fact that the secret of the success of the cen tralised unit is not its equipment but the concentrated experience of every member of the staff.

If the desirability of centralisation is accepted then the first question to consider is the size of the area which will carry an adequate and fully equipped organisation. I am going to quote English figures as I am familiar with them: cancer incidence, however, follows such a conventional pattern that they may be taken as giving a good general picture of the problem anywhere except where special etiological factors are operative, such as account for the skin cancer of Australia, or the mouth cancer in India. For each unit of population of 100,000 analysis of the figures show that the incidence of *new* cases of cancer is of the order of 200 new cases per annum. Of these 200, however, about a hundred are types of cancer for which as yet we have little to offer and which, unfortunately, must be regarded as already incurable when first diagnosed, though many of these even can be greatly palliated. Only approximately 90 are of the types for which successful treatment is possible. Of these, apart from skin cancer, the numbers of which vary greatly, the three important curable cancers, namely, breast, uterus, and mouth, constitute the following per *100,000 population:*

Breast	20 cases
Uterus	13 cases
Mouth	8 cases

With these figures in front of one it needs no clever argument to convince that several hundred thousands of population even is still too small a number by far to carry an efficient independent organisation. A Cancer Centre purely in terms of numbers of cases must obviously serve a large unit of population if it is to see sufficient numbers of each cancer type, not merely of cancer as a whole. This will often entail centralisation for a very wide area.

It is fair to say that all the studies of the last four or five years on thi subject by those British Authorities with special knowledge of the

problem[1] indicate that the minimum population number required to carry an effective and adequately equipped Unit is one million, but that efficiency rises even over that figure.

Let us accept this premise for a moment and consider the main functions and component parts of such a co-ordinated organisation. These are, talking very broadly, three:

1) The development of a centralised radiotherapeutic Institute;
2) The provision of a surgical treatment scheme of some type;
3) The provision of cancer diagnostic and clinic services for the area served.

Radiotherapy

Centralisation may mean anything from mere fusion of controls to complete localisation of a whole organisation to one site. For radiotherapy centralisation lies between these two extremes, its essentials being a unified staff and the provision in one place of all facilities for active treatment. This interpretation calls for a single building or group of buildings as the »Centre». The major component of this is, naturally, the wards in which the patient will be nursed during treatment; this can usually be referred to as the »Hospital» section of the organisation. Linked with it will be the two departments providing most of the facilities for treatment — the Roentgen therapy department and the Radium department. Even these three are, however, incomplete in themselves and the »Institute» only becomes a complete entity when out-patient services, facilities for collateral surgery, an integrated records system, a department of physics, and various ancillary departments, including radio-diagnosis, pathology, and photography are also provided.

As regards staff a striking characteristic of present day British practice is the adoption by most centres of a whole-time medical staff practising exclusively radium and roentgen therapy — the two cannot nowadays be divided. This whole-time staffing is in a sense forced on us as an indirect result of the expense and complexity of the plant and equipment and of the number of special services and skills which are required.

For the radiation departments particularly, centralisation is the only way to provide adequate material facilities. To carry a stock of

[1] »Organisation for the treatment of Cancer».
British National Radium Commission publication obtainable at 12 Manchester Square, London. W. 1.
»Planning of Radiotherapy for Great Britain».
Faculty of Radiologists publication, 1942, obtainable at 45 Lincoln's Inn Fields, London.

eve . minimal quantities of all the different types of radium which may be (alled for needs at least a thousand milligrams, and even this amount ten s to lack flexibility. As an example of this feature it is worth noting tha the Manchester Radium Institute now carries five different types of r dium needle of the one active length of 3 cms. Ownership limited to a mounts of 250—750 milligrams, only too often means making the pat nt fit the radium instead of the radium being selected to fit the pat nt. On the roentgen side there should be enough roentgen plants of eac necessary type to make it impossible for breakdown to interrupt trea ment, since interrupted treatment may well mean unnecessary deat h. Moreover, recent developments of radium beam units and high-volt ge roentgen plants introduce a factor of expense only justified if ther were a guarantee of sufficient patients to ensure full usage.

The setting aside of hospital accommodation for this type of work is not only necessary for centralisation of the special equipment, it is an asset in itself. Skilled radiotherapy nursing is as valuable as specialised medical knowledge. The following illustration from Manchester experience is a most educative example of this point. Before the Christie Hospital was built the Radium Institute's patients were scattered in twos and threes in all the surgical wards of the main teaching hospital. In spite of using a single theatre and treatment by the same radiotherapists, mortality from post-operative complications of mouth implants exceeded 10 %. In the recent war all this implant work was centralised to a single country annex with permanent nursing staff. In spite of war difficulties one full year was achieved without a single post-operative death. Nursing a busy radiotherapy ward is every bit as strenuous and requires as full a staff as an active surgical ward. One respect in which radiotherapy wards can, however, be adapted to their special function is to link them with »dormitory» or »hostel» accommodation for roentgen patients; these seldom need to be confined to bed and so require little real nursing for the initial stages of their treatment.

The records system is of great importance. The long term value of the provision of collected statistics of five years' results is widely recognised, but another, to my mind more important, function is often overlooked. Provided sufficient numbers of patients of each cancer type are treated each year good records of treatment allow reliable evaluation of new techniques in periods much shorter than five years. Assessment of a new technique illadvisedly adopted can often show well within a one-year period that it is a failure. Thus, one result of centralisation, which is specially important to a developing specialty such as radiotherapy, is the ability to study case groups of adequate size, not after a lapse of years to allow numbers to accumulate, but almost concurrently with the use of any particular technique.

Even with regard to the ancillary departments, the segregation of considerable numbers of patients of each type again makes for a high degree of specialised knowledge. A general pathologist, however good, can seldom compare in accuracy with one who has given special study to cancer histology and who has access to adequate material. For physics it is no longer too much to say that radiation physics — often referred to nowadays as hospital physics — has come to stay as an essential branch of physics and indeed a profession in itself. Only through a centralised department can the necessary training in this new field be provided.

To all these assets must be added the enormous advantage which a large organisation acquires from its ability to attract and support a research team as essential partners in the whole effort.

For a unit of population of two to three million, which is required to carry a fully effective centre such as this, it is, I believe, most undesirable that the organisation be developed as a section of one general hospital, except in rare instances. It is better as a separate Institute. Such are the natural rivalries of hospitals that far the best co-operation can be obtained by an independent unit with an autonomous Governing Board — a Board on which co-operating hospitals, the University and Government, Civic or Local Authority, can all be represented. Though autonomous in structure, however, such a unit has very much to gain by being situated near the University and, where possible, a general hospital as well.

Surgery

The surgery of cancer has heretofore invariably been decentralised as part of general surgery. A way must be found to make it a specialist branch of surgery with work concentrated to a limited number of surgeons. Progress will then be engendered through the extensive experience acquired by those persons involved. On the other hand, it does not seem desirable that surgical cancer becomes, like radiotherapy, an exclusive specialty. Rather should the malignant disease peculiar to each region be the responsibility of appropriate specialists, and the work so canalised that selected specialists see adequate numbers of cases each year. It seems to me[1] that it might well be laid down as an axiom that any surgeon engaged in an organised cancer service must be enabled to give at least half his working time to this special work, the remainder being in general surgery so as to maintain his wider field of experience. The same outlook should hold for the main associated specialties — otolaryngology, gynaecology and genito-urinary surgery. Admittedly this

[1] The Cancer Act: RALSTON PATERSON, *1942*, Lancet, Sept. 12; p. 317.

wo d mean that many men at present seeing small numbers of cancer cas , as part of their practice will be asked to agree to centralise that wo to *one* person. In the end, however, the matter should balance out as he selected man will yield up part of his ordinary work to make the necessary time.

While it is clear that all cancer surgery could profitably be completely cen alised, the medico-political situation often makes this difficult to atta n and it may well be that first stage planning should not aim beyond segr gation to the teaching and major key hospitals of an area. The ultimat ideal, however, is segregation to one special institute dealing both with surgical and radiotherapeutic cancer. If this were achieved the Institute would have to work in very close harmony with the local teaching hospital and almost certainly be staffed surgically by men also on that staff.

Even where a Cancer Institute is predominantly radiotherapeutic, a considerable amount of surgery is called for. In the appointment of surgeons, gynaecologists and other specialists for this purpose it is essential to keep numbers down to a minimum. Any scheme by which, for example, all the senior staff of a teaching hospital were ipso facto members of the Institute, would in practice be ineffective.

As I have indicated, the systematic organisation of surgical cancer services is difficult in many ways, so it is desirable to point out that whether the surgical work be co-ordinated or not, there is still a clamant need for an institute which, as a start at least, would co-ordinate the radiotherapy of an area and develop good cancer diagnostic centres.

Diagnostic and Clinic Services

The third main section of the proposed cancer service is the system of cancer diagnostic clinics. The pattern of these diagnostic services is one presenting interesting problem, especially in less populated areas. Simple centralisation such as I have urged as the only successful key to treatment fails to meet the real test of securing early examination and advice. A very different approach must be adopted. Diagnostic clinics to which local practitioners and local surgeons can refer all cases which may be cancer should be established in the hospitals co-operating in the scheme, to an extent which will ensure that few patients will have to travel any great distance to be reviewed in this way. These diagnostic clinics need not be elaborate in any way. Their purpose is merely to see and review cases and decide whether there is a need for them to come into the central organisation, either for further investigation or, in the more obvious cases, for treatment. A question often raised is whether these diagnostic centres should be staffed by local men or not. I person-

ally am firmly of opinion that the Clinic should be held by a visiting consultant or radiotherapist from the staff of the central Institute. For more isolated areas one visit a month meets the need though it is not ideal; for remote areas this could be done by air transport. For the clinics in the large hospitals once or twice a week is indicated. No treatments should be carried out in these clinics and the whole record system should be integrated with that of the Institute. The present Manchester-Lancashire arrangements illustrate this clinic pattern. The Christie Hospital and Holt Radium Institute provides radiotherapy for an area with about four and a half million population. Clinics are held at sixteen Hospitals in the area outside Manchester itself, and each month twenty-four clinics are conducted by members of the staff. This is additional to the large daily clinics at the central Institute itself in Manchester. This *decentralisation* of clinics is, however, still in the *functional* sense *centralisation* as they are administered and staffed from the central cancer control unit.

Development Problems

So much for the general principles involved in this question of cancer centralisation. When the attempt is made to apply them in a previously unorganised area certain difficulties are almost invariably encountered. These include the following:

1. Uncritical acceptance of the surgery of cancer as an integral part of general surgery. The advantages to be gained from genuine surgical team work associated with narrow specialisation of each individual's operative contributions are still inadequately realised. Application of Mayo Clinic principles to the cancer field would yield a rich harvest, and could be ensured by making appointments to cancer hospitals only for specified fields.
2. The extreme scarcity of beds specifically allocated for radiotherapy. A considerable number may even be found reserved for incurable cancer cases while patients who might be treated and given a chance of cure are either delayed till their chances of successful treatment become negligible. If a ruthless choice has to be made because of real stringency surely treatment has absolute priority.
3. Both roentgen and radium work already established on a small scale in a number of different hospitals in the area. These instinctively oppose absorption, so that considerable effort has to be made to convince them that they can meet their obligations to their patients far better by taking part in a co-ordinated scheme than by individual planning.

4. The custom under which in many countries roentgen treatment is still centred with radiodiagnosis, and radium with surgery. Real advance is now impossible till these two be fused into the separate and distinct specialty of radiotherapy.
5. The primitive co-ordination of hospital planning in many areas. This makes the initiation of new schemes difficult because of the lack of an over-riding authority and of the need therefore to create first some form of joint authority for this special purpose.
6. The vested interest of individuals in maintenance of status quo. This can sometimes be countered by a generous outlook towards compensation or by judicious transition period appointments.

These are, I believe, the facts. It is only where real good-will and a desire for improved services exist that these difficulties can be successfully surmounted. The collaboration of many people is necessary wherever it is decided that plans be set afoot to develop either a cancer or a radiotherapy institute to serve an extensive area as an exclusive centre. Yet it is so well worth doing. It must be remembered too that organisation is just as important as buildings. The diagnostic centres have to be developed, the staff has to be collected and integrated into a team, and the whole general machinery got going. Even where new building is difficult, therefore, it is still worth while to go ahead with an interim scheme using accommodation already available. As a general rule things which grow up are sounder and more stable than things made big from the beginning. Many of the recent improvements in English practice have been based not on new Institutes, but on the use of very simple accommodation built in the emergency of war as casualty wards and now superfluous. The changes taking place in England in this field are taking place fast and there is in most matters of this kind a tide in the affairs of men which, taken at the turn, leads to fortune. In the field of radiotherapeutic organisation we are, I hope, at such a turn of the tide.

SUMMARY

The results of cancer treatment can be greatly improved by centralisation of all treatment facilities. This calls for the provision of a single »Centre« for population aggregates of upwards of one million with improving efficiency up to two or three million. The structure and functions of such a centralised unit are discussed.

ZUSAMMENFASSUNG

Die Resultate der Carzinombehandlung können durch Zentralisierung aller Behandlungsmethoden wesentlich verbessert werden. Dies erfordert die Schaffung je eines

Zenters für mehr als eine Million der Bevölkerung mit zunehmender Leistungsfähigkeit bis 2—3 Millionen.

Die Struktur und Funktion einer solchen zentralisierten Einheit werden besprochen.

RÉSUMÉ

Les résultats du traitement du cancer peuvent être grandement améliorés par la centralisation de toutes les facilités de traitement. Ceci demande la provision d'un seul »Centre» pour les agglomérations d'une population de plus d'un million, avec une efficacité croissante jusqu'à deux ou trois millions.

La structure et les fonctions d'une unité ainsi centralisée sont discutées.

DU LABORATOIRE PASTEUR DE L'INSTITUT DU RADIUM, PARIS, SERVICE DE RADIOBIOLOGIE
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SUR LA DIFFÉRENCE DES LÉSIONS HISTOLOGIQUES PRODUITES, DANS LA PEAU DE LA SOURIS, PAR LES RADIATIONS ULTRAVIOLETTES ET PAR LES RADIATIONS ROENTGEN[1]

par

A. Lacassagne

Jusqu'ici, les applications de ce que nous avions appelé, avec HOLWECK, la »radiobiologie quantique» s'étaient trouvées confinées dans l'étude de cellules ou d'organismes inférieurs: protozoaires, levures, bactéries, virus, bactériophages. Les rigueurs expérimentales, devant permettre de comprendre le mécanisme d'action des radiations dans la matière vivante, exigeaient que l'on s'adressât à des éléments isolés, aussi semblables entre eux que possible, placés à égale distance de la source émettrice, exactement dénombrables par un procédé direct ou indirect.

Des recherches entreprises dans un tout autre dessein, avec FRILLEY et LATARJET, nous ont conduits à reconnaître fortuitement, dans un organe complexe comme l'épiderme de la Souris, le mode d'action quantique de diverses radiations électromagnétiques.

Voici d'abord le résumé de ces expériences, qui ont déjà été rapportées avec plus de détails dans une publication antérieure.[2]

I. Comparaison des Effets Produits, sur la Peau de la Souris, par des Radiations de Différentes Longueurs d'Onde

On a utilisé, dans ces expériences: le rayonnement ultraviolet total d'une lampe à vapeur de mercure à pression moyenne (2,500—3,650 Å); les rayonnements roentgen correspondant à 4 Å et 0.95 Å environ.[3]

[1] Remis à la Réd. le 6 Juin 1947.

[2] LACASSAGNE (A.) — *Proceed. roy. Soc. of med.*, t. 39, p. 605, 1946.

[3] a) Rayonnement d'un anticathode d'argent sous 4,500 volts, filtre Al 0.05 mm (raie L + fond continu);
b) Rayonnement d'une anticathode de molybdène sous 33,500 volts, filtre Al 0.05 mm (raie K + fond continu).

1°) ACTION DU RAYONNEMENT ULTRAVIOLET. — a) *Chez la Souris nouveau-née.* L'objet initial de la recherche nous avait orientés vers l'étude des réactions du tégument chez des animaux de 1 à 2 jours. La peau comprend alors: l'épiderme formé de 4 ou 5 couches de cellules et de squames cornées; le derme dans lequel commencent à s'enfoncer les bourgeons des futurs follicules pilosébacés; le plan musculaire du peaucier, compris entre deux membranes de tissu conjonctif lâche de l'épiderme. Cet ensemble s'étend, en profondeur, sur un peu plus de 200 μ.

Différents stades de la réaction consécutive à l'irradiation sur un champ de 6 × 5 mm au niveau de la région dorsolombaire, avaient été reconnus.[1] Ils correspondaient aux doses suivantes: seuil de l'érythème, 200 finsens; érythème franc, 600 f.; desquamation, 800 f.; épidermite exsudative, 1,000 f.; dermatite nécrotique, 1,500 f. (soit 90,000 ergs par mm²).

Ce dernier degré de lésion — et son mode de réparation — avaient été particulièrement étudiés.[2]

A l'examen microscopique de peaux prélevées après des temps de plus en plus longs après l'irradiation, on avait constaté: 1°) l'installation, en 48 heures, d'une nécrose diffuse, consécutive à la mort immédiate de tous les éléments jusqu'à une profondeur de 150 μ. Par conséquent elle portait, également et indifféremment, sur les cellules de l'épiderme, des bourgeons pilaires, du tissu conjonctif, des vaisseaux, des nerfs et — le plus souvent — du muscle peaucier; 2°) la réparation obtenue en 7 ou 8 jours, après élimination des tissus mortifiés sous lesquels s'était insinué, en partant des bords de l'ulcération, un épiderme néoformé.

b) *Chez la Souris adulte.*[3] La nécrose diffuse s'obtient de même, après administration de la dose de 1,500 f., sur un segment cutané de 1 cm² ayant été épilé une semaine auparavant. Dans ce cas aussi, la lésion s'étend jusqu'à une profondeur de 150 μ, au delà de laquelle l'intégrité des cellules est respectée. Mais cette distance ne correspond plus, chez un animal dont la peau a terminé sa croissance, qu'à un champ d'action intéressant l'épiderme et la partie immédiatement sous-jacente du derme. Dans ces conditions, la séparation entre les tissus mortifiés et ceux restés indemnes au-dessous de l'eschare, coupera transversalement, près de leur jonction avec l'épiderme, les follicules pileux dont le segment inférieur participera à la régénération d'un nouvel épiderme par la multiplication des cellules de leurs gaines. La cicatrisation sera achevée une douzaine de jours après l'irradiation.

2°) ACTION DU RAYONNEMENT DU MOLYBDÈNE. — a) L'irradiation à la dose de 3,000 r, sur une souris adulte, d'un territoire cutané de

[1] LACASSAGNE (A.) et LATARJET (R.). — *C. R. Soc. de Biol.*, t. 137, p. 413, 1943.
[2] LACASSAGNE (A.) et LATARJET (R.). — *C. R. Soc. de Biol.*, t. 137, p. 435, 1943.
[3] LACASSAGNE (A.) et LATARJET (R.). — *C. R. Soc. de Biol.*, t. 139, p. 4, 1945.

mê[illegible]es siège et dimensions que dans l'expérience précédente, n'a produit qu'[illegible]n érythème discret et la chute des poils vers le 20ème jour; l'épiderme n'a [illegible]présenté aucune modification apparente. On reconnait donc, ici, la ma[illegible]festation classique d'une action des radiations s'exerçant sélectiv[illegible]ment sur les cellules matricielles du bulbe pileux. Un autre exemple, enc[illegible]re plus démonstratif du phénomène d'inégale radiosensibilité des élér[illegible]ents cellulaires se constate dans les organes sous-jacents, ovaire et rein[illegible] situés à 5 mm de profondeur, et qui ont subi des dommages considér[illegible]bles et définitifs. Or, la dose reçue par ces organes ne représente qu'[illegible]viron 25 % de celle administrée à la surface du tégument, et qui corr[illegible]spondait elle-même à une énergie incidente d'environ 760 ergs par [illegible]mm².

b) En première approximation, l'établissement du bilan des lésions obte[illegible]nues dans ce cas et dans le précédent avec les ultraviolets, pour une même quantité d'énergie absorbée, fournit le résultat attendu:

nécrose totale de l'épiderme pour 90,000 ergs reçus par mm² de surface cutanée; intégrité pour 760;

absence de lésion au delà de 150 μ dans le cas des radiations ultraviolettes très absorbables; atteinte d'organes profonds dans celui des radiations roentgen plus pénétrantes.

3°) Action du rayonnement de l'argent. — On s'est alors proposé d'essayer de reproduire, avec les rayons roentgen, le type de lésion que les ultraviolets avaient fourni. Il semblait qu'il dût suffire, pour cela, d'employer un rayonnement moins pénétrant que K du molybdène, et dont l'absorption se réalise dans une épaisseur de tissu à peu près comparable à celle des ultraviolets.

Les mesures faites par Frilley et Latarjet montraient que, dans le cas de L de l'argent, le rayonnement est absorbé par la peau de Souris dans la proportion de 50 % à 15 μ, 60 % à 30 μ, 67 % à 50 μ, 75 % à 120 μ et 80 % à 150 μ. On s'approchait donc sensiblement des conditions du rayonnement fourni par la lampe à vapeur de mercure, pratiquement absorbé en totalité dans 150 μ.

Dans une première expérience, on chercha à reconnaître la dose permettant de réaliser une lésion cutanée présentant des caractéristiques proches de celles de la dermatite par ultraviolets. Pour des doses allant de 500 à 2,700 ergs par mm², on obtenait bien la formation d'une ulcération croûteuse, laissant à sa place après élimination une zone d'épilation (temporaire pour 500 ergs, totale et définitive pour les doses supérieures). Mais les réactions, apparemment moins sévères, se prolongeaient plus longtemps: érythème au 3ème jour, suivi de pigmentation; ulcération vers le 12ème; chute de la croûte vers le 16ème seulement.

De plus, le déroulement des lésions étudiées au microscope montrait un processus à tous égards différent, aussi bien dans la constitution que

dans la réparation des dégats. Au début, les altérations cytologiques, aussi précoces que dans le cas des irradiations ultraviolettes, ne portent que sur certains éléments particulièrement sensibles. On note seulement la disparition des mitoses dans la couche génératrice de l'épiderme et de nombreuses lyses des cellules dans les formations destinées à donner les follicules pileux et qui seront en partie détruites au 3ème jour. A cette date, les cellules épidermiques du revêtement présentent des anomalies et subissent en masse la maturation cornée. La dégénérescence de l'ensemble de l'épiderme ne s'achève qu'au 9ème jour. Cependant, le tissu conjonctif montre seulement de la congestion et une forte infiltration leucocytaire, sans destruction des éléments fixes.

On obtient donc, avec les radiations de 4 Å, la dégénérescence de l'épiderme par action élective sur les cellules de la couche germinative, c'est à dire par le même processus décrit par REGAUD et NOGIER dans la radioépidermite produite par des rayonnements roentgen de plus courtes longueurs d'onde.[1] En revanche, ce mode de destruction contraste avec la nécrose diffuse obtenue avec les rayonnements ultraviolets.

II. Essais d'Interprétation des Résultats Expérimentaux

1°) DIFFÉRENCE QUANTITATIVE DES IRRADIATIONS. — A priori, la raison de la différence observée entre les effets des rayonnements ultraviolets d'une part et roentgen de l'autre paraissait évidente: l'inégalité considérable de l'énergie absorbée dans les deux groupes d'expériences (90,000 ergs/mm² dans le premier cas, de 500 à 2,700 dans le second).

On a donc cherché à diminuer cet écart dans de nouvelles irradiations. Mais, comme des raisons techniques empêchaient d'augmenter l'intensité de l'irradiation de roentgen sans allonger sa durée de façon inadmissible, on a refait des séries d'examens histologiques portant sur des peaux de souris nouveau-nées, irradiées avec des doses moindres de rayons ultraviolets, jusqu'à 500 f. (30,000 ergs par mm²).

Même à cette dernière dose, qui n'entraîne macroscopiquement qu'un léger érythème, avec faible desquamation sans épilation, on a retrouvé, au 3ème jour, le même type de destruction diffuse des éléments cellulaires; seule la profondeur de l'atteinte variait. Pour 500 f., la nécrose ne s'étend pas au delà de quelques μ. Aussi, l'épiderme n'a-t-il pas été totalement détruit, de nombreuses cellules de la couche génératrice restant apparemment intactes, de même que les formations folliculaires dans lesquelles on ne reconnaît pas d'éléments en cytolyse; la vasodilatation et l'oedème du derme très marqués ne s'accompagnent pas de destruction des cellules conjonctives. La lésion rappelle donc celle obtenue avec 1,500 f. dans une peau de souris adulte.

[1] REGAUD (CL.) et NOGIER (TH.). — *Arch. d'électr. méd.*, t. 21, p. 49, 1913.

. la suite de ces constatations, on fut contraint d'éliminer l'inégalité des quantités de radiations comme cause principale des différences d'a ion observées, et de faire intervenir la qualité de ces rayonnements. Il : llut conclure que la destruction de l'épiderme par ultraviolets se réa e selon un processus histologique dissemblable à celui que déclanche les rayons roentgen, même au cas où le coefficient d'absorption dan les tissus est le même pour les deux rayonnements: dans le premier cas, une sorte d'effet de »tout ou rien» entraîne la mort cellulaire immé ate dans des couches de plus en plus profondes de tissu lorsque la dos augmente; dans le second, on retrouve, quelle que soit la longueur d'on le, l'effet sélectif bien connu, s'exerçant avec prédilection sur les cellu es des couches germinatives des formations épidermiques.

2°) Rôle de l'absorption quantique du rayonnement par les cellules. Il semble, comme l'a suggéré Frilley, que nos résultats obtenus sur la peau de la Souris fournissent un exemple de l'action quantique des rayonnements, telle qu'on l'interprète d'après la théorie de l'impact: Une seule ionisation, produite par un électron secondaire à l'absorption d'un photon roentgen, au cours de son passage à travers la cellule, suffirait à tuer un élément germinatif des formations épidermiques; le même effect ne se manifesterait qu'après l'absorption de plusieurs photons U.V.

Il se produirait, pour la cellule-souche épidermique, ce qu'Holweck et Lacassagne avaient admis dans le cas de la Levure *Saccharomyces ellipsoideus*,[1] et ce que Latarjet a confirmé avec une grande précision pour ce même objet[2] et pour le bacille dysentérique Y6R.[3] Ce dernier chercheur a établi que l'arrêt de multiplication du bacille est obtenu par une seule ionisation dans le cas des radiations roentgen du molybdène, ou par l'absorption de 5 photons U.V. de 2,537 Å; l'arrêt de la division après 24 heures chez la Levure par 2 ionisations roentgen, ou par l'absorption de 10 photons U.V.

Afin d'étayer l'hypothèse émise à propos de la différence des réactions de la peau de la Souris, Frilley et Royer[4] ont imaginé une technique permettant d'étudier en profondeur l'effet respectif des deux rayonnements sur une culture microbienne, ce qui n'avait pu, jusqu'ici, être réalisé avec précision que sur des cultures en surface.

Irradiant le paradysentérique Y6R, comparativement avec les mêmes radiations roentgen du molybdène et les ultraviolets de 2,537 Å, ils ont pu rendre évident que le nombre des cellules survivantes augmente

[1] Holweck (F.) et Lacassagne (A.). — *C. R. Acad. des Sci.*, t. 190, pp. 524 à 527, 1930.

[2] Latarjet (R.). — *Ann. Institut Pasteur*, t. 70, p. 277, 1944.

[3] Latarjet (R.). — *Ann. Institut Pasteur*, t. 69, p. 205, 1943.

[4] Frilley (M.) et Rouyer (M.). — *Ann. Institut Pasteur* (sous presse).

progressivement en fonction de la profondeur dans le milieu irradié par les rayons roentgen, tandis que la séparation reste nette entre une zone stérile et une zone intacte dans les milieux soumis aux U.V. Lorsqu'on augmente la dose des radiations ultraviolettes, l'aspect des préparations n'est pas modifié, mais la transition entre les deux zones se place à une profondeur de plus en plus grande.

Comme les courbes de mortalitè obtenues dans ces expériences coïncident avec celles de LATARJET, on a donc la démonstration que la différence d'action des deux rayonnements, lorsqu'ils s'exercent en profondeur sur le bacille, ressortit au même phénomène mesuré dans le cas des irradiations en surface, c'est à dire à la nécessité d'absorption de plusieurs chocs U.V. avant que ne se produise l'effet exercé par un seul choc en cas de rayons roentgen.

Il n'est évidemment pas permis d'établir une assimilation complète entre ce qui se passe dans une culture pure d'une espèce cellulaire, et dans le complexe d'éléments variés et plus ou moins intriqués que représente une peau de souris. Néanmoins, si l'on fait abstraction des grandes variations des radiosensibilités propres à chacune des espèces cellulaires, pour n'envisager qu'un effet moyen, la comparaison se justifie. Les répartitions des léaions dans l'espace se ressemblent, qu'on les examine sur des coupes d'un bloc de gélose contenant des bactéries incluses dans la masse, ou des coupes de peau de souris: dans les deux cas, on constate un effet progressivement décroissant en profondeur avec des radiations roentgen, nettement limité avec les rayonnements ultraviolets.

Une autre analogie ressort des données quantitatives ci-dessus mentionnées. On a vu que, pour produire des effets macroscopiques comparables à ceux des rayonnements roentgen de même absorption (4 A), les ultraviolets doivent être administrés à des doses très supérieures (90,000 ergs/mm² contre 500), ce qui prouve un »rendement» moindre de ces dernières radiations. Or, chez une bactérie comme chez une levure, LATARJET a démontré que les photons U.V. absorbés, porteurs d'une faible énergie (4 ou 5 volts), ont une probabilité d'induire l'effet primaire — autrement dit, un rendement — environ 200 fois moindre que la probabilité d'action de l'ionisation, porteuse d'une énergie plus élevée (33 volts). Il est remarquable que l'on retrouve un rapport des énergies du même ordre dans le cas de l'irradiation de la peau de Souris avec ces deux rayonnements.

RÉSUMÉ

Il n'a pas été possible de réaliser, dans la peau de la Souris nouveau-née, une même lésion histologique en utilisant comparativement les rayonnements ultraviolets et les rayonnements roentgen de 4 A, bien que les absorptions en profondeur soient sensiblement équivalentes dans les deux cas. Les ultraviolets produisent une nécrose totale des élements, nettement limitée à une profondeur plus ou moins grande selon la dos. Les

lés[illegible]s produites par les rayons roentgen sont toujours électives et progressivement déc[illegible]issantes dans l'ensemble.

Ni les inégalités dans la quantité d'énergie fournie par les techniques d'irradiation uti[illegible]ées, ni — probablement — le mode d'absorption moléculaire des ultraviolets et ato[illegible]ique des rayons roentgen, ne paraissent suffire à expliquer la différence si marquée dan[illegible] les lésions histologiques produites.

Par comparaison avec les résultats d'expériences antérieures, faites avec des organis[illegible]s inférieurs, on a été conduit à l'interpréter d'après la théorie de l'impact, comme une [illegible]conséquence du petit nombre d'ionisations nécessaires pour tuer les cellules avec les ray[illegible]nements roentgen (sans doute une seule ionisation dans le cas des cellules des bourgeo[illegible] pilaires), par comparaison avec un nombre toujours plus élevé de photons U.V. deva[illegible]t être absorbés pour aboutir au même résultat.

SUMMARY

It has not been possible to obtain in the skin of the newborn mouse an identical histological lesion by comparative exposure to ultraviolet rays and to roentgen rays of 4 A, although the absorptions in deepness disclose sensible equivalence in both cases. Ultraviolet rays produce total necrosis of the elements, distinctly limited to a more or less profound extension according to the dose. The lesions conditioned by roentgen rays are always elective, and in their entirety progressively decreasing.

Neither inequalities in the energetic supply provided by the different technics of irradiation, nor — probably — the mode of molecular absorption of ultraviolet rays and the atomic one of roentgen rays seem to insure explanatory evidence of the marked difference between the ensuing histological lesions.

Taking into account the results of prior experiments gone through on inferior organisms, one has been conducted to interpret the matter according to the »impaction» theory, as a consequence entailed by the small number of ionizations necessary to destroy the cells by use of roentgen rays (undoubtedly one single ionization in the case of pilary bulbs), in comparison with always more numerous ultraviolet photons required for absorption to secure the same end result.

ZUSAMMENFASSUNG

Es war nicht möglich, in der Haut der neugeborenen Maus durch vergleichende Anwendung von teils ultravioletter Bestrahlung, teils Röntgenstrahlen A 4 die gleichen histologischen Schäden zu setzen, obgleich die Tiefenabsorption in beiden Fällen einigermassen gleichwertig war. Die ultravioletten Strahlen erzeugen eine Totalnekrose der Gewebselemente, die streng auf eine je nach der Dosis mehr oder weniger grosse Tiefe begrenzt ist. Die durch die Röntgenstrahlen erzeugten Schäden sind immer elektiver Natur und nehmen im Gesamtbilde mehr und mehr ab.

Weder der Unterschied der durch die gebrauchte Bestrahlungstechnik gegebenen Energiemenge noch — wahrscheinlich — die Art der Absorption, bei den ultravioletten Strahlen durch Moleküle, bei den Röntgenstrahlen durch Atome, scheint die so ausgesprochenen Unterschiede der erzeugten histologischen Schäden erklären zu können.

Durch Vergleich mit früheren Versuchen an niedriger stehenden Organismen ist man dazu gekommen, dies nach der Anpralltheorie als eine Folge der geringen Zahl der Ionisation zu erklären, die erforderlich sind, um die Zellen mit Röntgenbestrahlung zu töten (zweifelsohne eine einzige Ionisation bei den Zellen der Haarwurzel), im Vergleich zu der jedenfalls grösseren Anzahl von ultravioletten Lichtpartikeln, die absorbiert werden müssen, um das gleiche Resultat zu geben.

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CAPACITIVE ELECTRIC CHARGE AS A BIOLOGICALLY ACTIVE ELEMENT IN ROENTGEN TREATMENT OF ORGANIC TISSUE[1]

(Preliminary report)

by

Carl Wegelius, M. D.

Starting from the hypothesis that variations in the capacitive charge of organic tissue stand in connection with the varying sensitivity to rays of such tissues, which has previously been observed and reported, various experiments have been performed, which seem to furnish surprising and interesting aspects. The experiments, one of which is related more in detail below as a type example, have been carried out in such manner that the capacitive charge in the subject of the experiment has artefact been increased by electric contact with a net of wires conducting a high-tension current. Simultaneously, the experimental material has been roentgen irradiated with a therapeutic dose known to release therein macroscopically readable biological effects. The experiments have been carried out separately, with exactly the same roentgen dosage, so that the experimental material has been capacitively charged with positive and negative electricity. For the sake of control the same roentgen dosage has then been administered to similar subjects without their having been artefact capacitively charged with electricity. Finally, also for the sake of control, similar subjects of experiment have undergone further culture, in part without previous roentgen irradiation, after merely equally strong and lengthy capacitive charging with respectively positive and negative electricity as in the foregoing cases, in part without either previous roentgen treatment or capacitive charging. The further culture of the subjects of the experiments, after the end of the experiments, as also the culture of the controls, has naturally been carried out under exactly similar external conditions. — Such experiments have been carried out

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on ifferent organic living objects such as peas and beans in the germi tive stage, with observation of their growth after the experiments, on ıltures of bacteria with regard to their increase and on white rats wit regard to the epilation effect. A type example of the carrying out of the xperiment and the results thereby obtained is given in detail below.

Experiments with growing peas

rdinary so-called field peas (Pisum sativum) were used as subjects of the experimen in this case. These have also been used by JÜNGLING in biological irradiation tests and ave then been found to be »lethally» injured by a roentgen dosage of 900 r. — In each of 4 Petri dishes 100 peas were set to germinate. A quite thin layer of cellulose wadding, saturated with a nutritive solution of the following composition was placed in the bottom of the dish: 1,000 ml water from the public mains, 250 mg KCl, 250 mg $Ca_3(PO_4)_2$, 250 mg $CaSO_4$ and 394 mg $MgSO_4$.

The peas were roentgen irradiated at the stage, when the root of the peas had attained a length of 2—7 mm, which was the case on the third day of growth. To the peas in the dishes 1, 2 and 3 900 r., measured in the air, were then administered, with 120 kV, 4 mA and 1 mm Al-filtration, while the peas in dish 4 were left untouched and served as controls. For the roentgen treatment the peas were taken out from the Petri dishes together with the saturated cellulose wadding described above and were placed in a single layer on a copper plate well insulated from the substructure (suspended by cotton threads 170 cm in length at 80 cm distance from the nearest earth, *i. e.* the floor). This copper plate was united by copper wire in good contact to the open non-insulated high-tension wire (close to, but outside the roentgen tube) on the respective anode- and cathode-sides of the tube during irradiation of the peas in dishes 1 and 3. A capacitive electric charge of the tension 120 kV and current strength 4 mA indicated for the roentgen treatment must therefore be present in the copper plate with respectively positive electricity for dish 1 and negative electricity for dish 3. Owing to the presence of a considerable con-

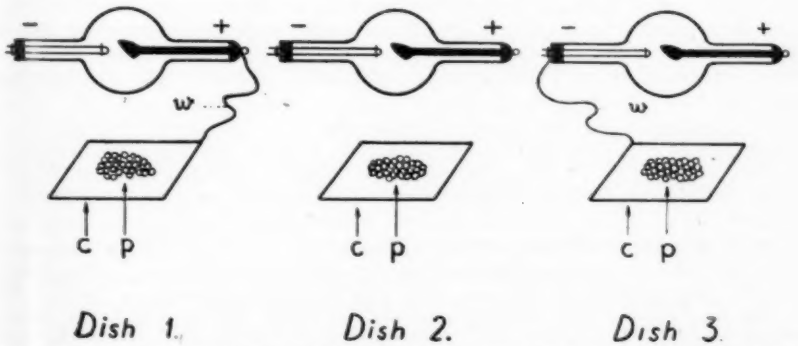

Fig. . Diagram showing the application of capacitive electrical charge by wire (w) from he roentgen tube to the different copper dishes containing the peas (p) subjected to ro atgen treatment (900 r). Dish 1 has a positive capacitive charge, dish 2 no charge, and dish 3 a negative capacitive charge.

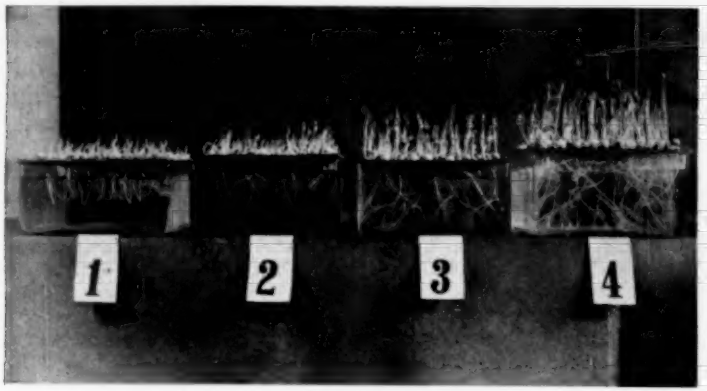

Fig. 2. The difference in growth of the peas in dishes 1—3 five days after treatment (all irradiated at the same time with 900 r) is clearly visible as regards the stems of the plants and the root-system. The peas in dish 1 (positive charge during treatment) are most damaged, the peas in dish 2 (no charge during treatment) are less damaged, while the peas in dish 3 (negative charge during treatment) are damaged least of all. — The control peas in dish 4 (not irradiated) have not been affected.

tent of salt and the electric conducting power due thereto in the nutritive solution in which the soaked peas, via the wet cellulose wadding, were electrically connected with the capacitively charged copper plate, the peas themselves must be regarded as being capacitively electrically charged in the same way as the plate. The application of the electric charge is schematically represented in fig. 1. — The peas in dish 2 were roentgen irradiated in the same way and with the same dosage as the two foregoing instances, but without the copper plate now being connected with the high tension net, thus without an artefact capacitive charge. — If a chemical or any other effect emanating from the copper plate and acting on the organic experimental material had been present (SEUDERLING), the gradual effect thereof was eliminated by the experimental conditions being similar in all three cases.

The experiment was thus intended to bring about a strong, respectively positive and negative artefact capacitive electric charge in the peas from dishes 1 and 3, at the same time that these were roentgen irradiated with a dosage, which, according to JÜNGLING, *ought to have a lethal effect on both these peas and those in dish 2, which was not capacitively electrically charged.*

After the roentgen treatment all the peas, also the controls, were transferred, retaining their grouping, to so-called culture dishes, numbered in the same way, in which dishes each pea was separately placed over a small hole in a cardboard covering the dish, with its roots reaching down to the interior of the dish, which was filled with the nutritive solution described above.

The results of the irradiation and the simultaneous artefact capacitive charge in the case of the dishes 1 and 3 were not notably observable during the two first days, which obviously corresponded to the latency period of the ray effect. However, on the third day after the roentgen treatment an obvious difference was already to be observed.

Th peas in dish 1 with a positive capacitive charge were found to be most strongly aff ted by ray injury, their growth stopped almost entirely, while the growth in dishes 2 a 3 was somewhat less affected in series. The control peas in dish 4 continued to grow qu undisturbedly. ——— During the following days the differences became still pla er, also in series. The peas in dish 1 withered away almost entirely, while those in dis 2 continued to grow slightly, and those in dish 3 still a little more. A photograph, fig. , of the plainly numbered dishes clearly shows the differences described above, with reg d to the stem of the plant and the root system.

The result of these experiments shows that the capacitive positive electric charge has inc sed and the corresponding negative charge has diminished the deleterious effect due to t roentgen treatment, when compared with the same irradiation without an accompanying cap itive electric charge.

The results of the experiments carried out in the manner described abo e, both in respect of growing peas and other organic test subjects used, appear to speak for the following biologically remarkable effects of irradiation.

1. A capacitive electric charge with high-tension electricity in the subject of the experiment simultaneous with the irradiation, appears to *further the deleterious effect* of roentgen, as compared with the effect of the same ray dosage when administered without such a charge.

2. A capacitive charge with negative electricity, simultaneous with the irradiation, seems to *diminish the deleterious biological effect* when a comparison similar to that in clause 1 above is made.

3. Capacitive charging with electricity in the same way, but *without* simultaneous roentgen irradiation has no biological effect whatever, irrespective of whether the experiment takes place in connection with a high-tension net as regards positive or negative electricity.

The foregoing apparently remarkable biological effects must naturally be thoroughly checked by numerous repeated experiments under varying, exact conditions, and with different subjects of experiment before they can be regarded as generalised, reliable and utilisable for further scientific speculations and practical application. With this aim in view the writer is himself engaged in extensive checking experiments of different kinds. — The reason why these experiences — though based hitherto on somewhat scanty material and only checked in a comparatively slight extent — are published already now at this early stage, is the wish of the writer to place without delay at the disposal of scientific research his observations relating to a ray-biological effect which may possibly be present and in such case is hitherto manifestly unknown.

A preliminary report of this kind is not suited for more detailed hypotheses as to how such a biological, ray-injury furthering effect of a positive capacitive charge and a ray-injury hindering effect of a negative

capacitive charge can be thought to arise. Some suppositions, merely indicated below, may, however, be put forward. — According to LEA, the biologically active ionisation which arises in the material under the influence of roentgen is to be regarded as being in practical respects only of a positive electric nature. Both LEA and CATCHSIDE, as well as GRAY, FAILLA, FANO & DEMERIC and also HENSHAW stress in their most recent publications the exceptional importance which must be ascribed to even apparently slight disturbances in the interior balance of the atoms caused by roentgen-rays as regards secondarily arising latent or manifest injury to the vital centres of the cell. A noteworthy contribution in this respect has been given by FORSSBERG. He has by irradiating Drosophila eggs with roentgen and gamma-rays found that the average mortality rate in a magnetic field increased 16.8 %.

If one starts with the assumptions that the particles split off from the atoms by ray influence in photo- and Compton effect are electrically negative and that the biologically active ionisation is to be regarded as electrically positive, it appears as if a capacitive positive electric charge present in the experimental material simultaneously with the irradiation could be thought to further the radiological ray effect, at least in the surface layer of the experimental material. Theoretically it might also be thought that such furthering effect could spread from the surface chainwise towards the interior. The living biological tissues must, as far as electrostatic conditions are concerned, in all probability be regarded as extremely sensitive and easily affected. — In the same manner a negative electric capacitive charge could be thought to influence the radiological effect in the contrary direction and thus have a diminishing influence thereon. — In analogy with the above, it is also theoretically conceivable — should these hypotheses prove to be well-founded — that a furthering or diminishing effect of ray influence could also be achieved through the introducing of the experimental material into a sufficiently strong magnetic field.

To Messrs. NOSCHIS, PEHRSSON and CEDERQVIST, Civil Engineers, my assistants in the experiments, which in technical respects often were very difficult to carry out, and to Mr. RAUTANEN, M. A., who at the Biochemical Research Institute has carried out and checked the plant-biological part of the work, to Dr. KAJ SETÄLÄ, who has provided animal material for the experiments and to Dr. KÖHLER who has placed roentgen apparatus at my disposal, I beg to express my best thanks for their valuable aid.

SUMMARY

A description of a possibly existing peculiar biological effect of roentgen irradiation on ving organic experimental material in connection with simultaneous artefact contri d capacitive electric charge. The effect, which appears to have a furthering action in a c leterious direction with a positive electric capacitive charge and a corresponding din nishing action with a negative electric capacitive charge, must be further checked wit the use of more material before it is available for generalized scientific speculation and practical application.

ZUSAMMENFASSUNG

Beschreibung einer möglicherweise existierenden besonderen biologischen Wirkung von Röntgenbestrahlung auf lebendes organisches Experimentmaterial bei gleichzeitiger künstlicher elektrischer Ladung. Die Wirkung, die bei positiver elektrischer Ladung in zerstörender Richtung verstärkt und bei negativer Ladung abgeschwächt zu werden scheint, muss noch durch Untersuchungen an weiterem Material bestätigt werden, ehe sie zu allgemeinen wissenschaftlichen Erwägungen oder praktischem Gebrauch verwendbar ist.

RÉSUMÉ

Description des effets biologiques particuliers, dont l'existence est vraisemblable, de l'irradiation par rayons roentgen d'un matériel expérimental, organique et vivant, muni artificiellement d'une charge électrique. Ces effets qui, avec une charge électrique positive ont une action augmentant et avec une charge électrique négative une action correspondante diminuant dans le sens de la détérioration, doivent être encore contrôlés sur un matériel plus grand avant qu'on puisse s'en prévaloir pour établir des théories scientifiques de portée générale ou pour en déduire des applications pratiques.

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TREATMENT OF CERVICAL CANCER[1]

by

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The rythmic cycles in which so many happenings in the universe occur, probably following a law of nature — the change from day to night, the tidal waves of the sea, the rythm of the seasons — can also be noted in medicine, not only in the variation of frequency and character of diseases, but also in the methods of fighting them. These cycles are distinctly recognizable in our methods of fighting cervical cancer. The present review intends only to describe the most important landmarks which led to the development of the different methods of treatment. It claims by no means to give a complete list of all the authors who have worked successfully on that problem.

The first attempts to treat cervical cancer by vaginal hysterectomy have shown very poor results. The history of the radical operation of cervical carcinoma begins 1878 with Dr. W. A. FREUND's suggestion to perform laparotomy and if necessary to extirpate carcinomatous glands. Since that time laparotomy gained steady recognition although vaginal operation has been resorted to again and again by some gynecologists.

It was WERTHEIM who in the first decade of this century performed his laparotomy for cervical cancer with extirpation of the glands systematically in hundreds of cases. He succeeded in considerably improving the permanent salvage so that the Wertheim operation soon conquered the world, and the vaginal operation was abandoned. Indeed, WERTHEIM and the surgeons who followed his example obtained absolute cures of 18—20 %.[2] The relative cures amounted to about 40 %.

[1] Submitted for publication, June 17, 1947.

[2] Cancer statistics are not easy to compare and evaluate because the authors unfortunately use different terms in their classification of cases and in reporting the percentage of cures. In the author's statistics the term absolute cure or salvage means like in HEYMAN's reports the five years survival of all cases seen by the author, not on / of

thi certainly being a definite improvement compared with the poor res ts of the vaginal and not radical abdominal operations. However, this im ovement had been achieved with great sacrifices. In the hands of the mo successful surgeons (WERTHEIM, BONNEY) the operative mortality ran ed between 15 % and 25 %. It was this enormous mortality and the dis tisfaction with the low number of permanent cures which in the sec id decade of this century prompted the Frenchmen WICKHAM, DE AIS, CHERON and RUBENS-DUVAL, the Germans DOEDERLEIN, KR NIG and BUMM, KELLY and BURNAM in the U. S. A. to treat cancer not surgically, but with radium or mesothorium, later on with roentgen ray (SEITZ, WINTZ).

In France REGAUD used the technique of massive doses, in the U. S. A. GRAY WARD, HEALY, the MAYO Clinic, SCHEFFEY and others developed and perfected irradiation which at present with varying methods is being used practically all over the world.

It is the merit of HEYMAN who since 1914 has worked incessantly at the perfection of radiation technique that the so called Stockholm method has in a series of more than 4,000 cases not only matched but even surpassed the percentage of the cases salvaged by operation. His work is outstanding not only by his achievement in cures but also by the humane and medical care he takes of his patients, the perfect organization of his Radiumhemmet and by the extraordinary follow up of patients; he has hardly lost track of a single one of his patients.

In general, radiation could soon match the results of operation and the mortality is very low compared with the high mortality of laparotomy.

With these results the courageous pioneers of irradiation, HEYMAN at the head, have earned everlasting merit and have really inaugurated a new epoch in the treatment of cervical cancer, the »treatment without operation». However, the conclusion drawn by so many that cervical cancer should not be operated any more but only treated by radiation never seemed justified to the author.

It has been proved that with radiation a number of patients with inoperable cancer can be cured who without radiation would have been irretrievably lost. It is true that the primary mortality after radiation is much lower than the death rate after laparotomy. Yet, comparing the final results it must be said that radiation could not keep more women alive than operation. Considering that dissatisfaction with the poor

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the t eated, including operable and inoperable cases, while the relative salvages mean the p rcentage of operated or radiated cases alive and without signs of cancer after five years Hopeless cases or patients who refused treatment are not excluded. All cases we lost rack of and patients who died from intercurrent diseases before five years elapsed are c unted as recurrences, even if the autopsy did show that no cancer was present.

results of operation was the only reason to abandon surgery, it was the author's belief that one should not rest satisfied to save with radiation the lives of just as many *i. e.* just as few women as were helped by surgery. In radiation we certainly possess a second and potent weapon to fight cancer; whether it is a better one than surgery always was and still is controversial.

Radiation has two outstanding achievements: 1) We can not only prolong life but we can even save lives in inoperable cases by radiation, where we were absolutely helpless formerly, so that the patients were doomed to suffer and to die. 2) The mortality rate of radiation treatment is low compared with the high primary mortality of laparotomy. But it must be repeated that not more lives have been saved by radiation than by surgery.

This latter statement does not imply any undervaluation of the extraordinary achievement of radiation therapy, but the fact that in spite of the additional number of inoperable cases cured by radiation, the total number of absolute salvages — as world statistics show — just equals the total number of cures by operation seems to indicate that surgery in a number of operable cases is superior to radiation. Therefore, gynecologists who believed in their surgery naturally tried to increase the number of permanent cures by operating also on progressed cases. We did that in the Schauta Clinic in Vienna and we were so radical that the operability for a period of several years increased from 50 % to 78 %. The expected success was not forthcoming. With our increasing radicalism the mortality increased but the number of permanent cures did not improve. LATZKO who made the Wertheim operation more radical had so high a mortality that nobody performed his operation, which theoretically had a good foundation, and even the excellent work of BONNEY suffers from high mortality. In U. S. A. LYNCH and TAUSSIG tried to be more radical than WERTHEIM but soon turned to a combined method of treatment. Considering these facts, most gynecologists gave up hope to improve the results of surgery by extending the indications for operation.

We all know exactly where the lever really must be applied to improve the results of cancer treatment. Statistics of both methods of treatment — operation and radiation — agree in one point: in early detected cases we can save up to 90 out of 100 patients, but the results become worse the further advanced the case is.

Therefore, the problem is the same to-day, as it always was, *i. e.* to make the diagnosis of cancer in the early stage in order to institute treatment as early as possible. Various efforts have been made to serve this purpose. The biological cancer reactions (ABDERHALDEN, FREUND, MEIOGSAGMIN) are not reliable. The colposcope and the Schiller test did not give

the results one had hoped for. The colposcope is of no value in the hands of the unexperienced and not necessary for the experienced in most cases. The Schiller test has some value for the practitioner, although a positive test does not indicate malignancy but only the presence of abnormal epithelium. The women with positive Schiller test should be referred to an experienced gynecologist and no diagnostic procedure should be made by the general practitioner. It would be necessary to instruct the general practitioner not to undertake efforts (biopsy etc.) to ascertain the diagnosis of uterine cancer but to refer every woman whose history arouses suspicion of malignancy to a cancer clinic or to an experienced gynecologist.

The author tried to institute the regular examination of healthy women in Austria at intervals of 4—6 months and he suggested the cooperation of insurance companies and the »Krankenkassen» (compulsory health insurance) for this purpose as early as 1924, without succeeding in his efforts. It is very fortunate that this country has been more successfull thanks to the collaboration of the lay public with the medical profession. The great value of periodic pelvic examination has been proved by McFarlane and her co-workers and others. Her indefatigable efforts are certainly of great help in our struggle against cancer. New methods to achieve early detection of uterine cancer by examining the vaginal smear (Papanicolaou, Meigs, Fremont-Smith and their co-workers, Ayre) are promising. The cytological diagnosis from the smear however needs great experience and can only be made in clinics and laboratories by specially trained men.

Having little success with our efforts to establish early diagnosis of malignancy we had to search for other means to improve the results of both methods of treatment, operation and radiation. Theoretically, this could be achieved in two different ways. 1) By diminishing the mortality of operation, 2) by combining radiation with surgery. Both ways have had the test of time and we can to-day examine and evaluate the results. Schauta in Vienna chose the first way. His »extended vaginal operation» achieved the same number of absolute cures as the most successful laparotomists (about 20 %). The mortality of 1,225 extended vaginal operations averages 5.7 % but was in the last 750 cases 3.9 % which is only slightly higher than the mortality of radiation (averaging 2—4 % in different statistics) but much lower than the 11—25 % mortality of laparotomy.[1] The incidence of lesions to ureter and bladder and rectum was much smaller than in laparotomy. Our rate of mortality is remark-

[1] The 1,225 cases were operated in the I. Universitäts-Frauenklinik in Vienna under Schauta and later under the author till 1920, from 1921—1937 in the author's gynecological departments of the Wilhelminen-, Rudolf- and Elisabeth-Spital including all the author's private patients.

ably low considering that more than 90 % of these operations were performed at a time when penicillin and the sulfonamides were unknown (the Prontosil had only been used within the last years). Peritonitis which was the primary cause of mortality in laparotomy has been avoided in most cases because in the vaginal operation the abdominal cavity and the bowels had to be exposed only for a short time. In the author's modification of the original Schauta method the greatest part of the operation is performed extraperitoneally, and the peritoneal cavity has to be opened for a few minutes only. Furthermore in the last 400 cases we never used inhalation anesthesia but only local anesthesia in twilight sleep with Scopolamine and Dilaudid and since 1933 also intravenous anesthesia (Evipal). This also helped to reduce shock and mortality. Our low incidence of ureter fistulae is explained by the fact that the blood supply to the ureter is not seriously disturbed as the upper arteries are never cut. The ureters are never seen hanging naked in the air like telegraph wires as in laparotomy. With the exception of the most distal part about 2—3 cm from the entrance into the bladder the ureters remain attached to their peritoneal cover — thus their blood supply is not impaired.

Our vaginal operation certainly at least equals laparotomy in the radical extirpation of parametrium and vagina but does not attempt one aim of laparotomy namely the extirpation of all carcinomatous glands. The importance of this point is still controversial.

SCHAUTA thought not much could be gained by laparotomy with the attempt to remove lymph glands, because there exists a direct communication from the posterior wall of the vagina and the cervix along the utero-sacral ligaments to the posterior pelvic wall and to the sacral and subaortic glands. These may be involved before the glands in the pelvis, which was proved in our hospital by complete microscopical examination of all the glands of patients who died from cervical cancer. Even if the iliac glands are removed the inaccessible subaortic and aortic lymph glands may already be involved.

Some authors claim that only a small percentage of cases where carcinomatous glands were removed, remained free from recurrence after five years, while others (BONNEY, LYNCH, TAUSSIG, MEIGS et al.) maintain the opinion that the extirpation of glands is important and could salvage for five years or more a number of patients where cancerous glands had been removed by laparotomy. The admission that neither local application of radium nor a vaginal operation could compete with laparotomy as far as the glands are concerned has always been a weapon in the hands of the laparotomists. But the proven fact that radiation treatment as well as the extended vaginal operation do match the results of laparotomy seems to indicate that the extirpation of glands is no sufficient reason to risk the dangerous laparotomy and that in radiation as well as in

ou: vaginal hysterectomy, the low mortality more than outweighs this pos ible advantage of laparotomy.

Even matching the permanent cures of laparotomy with so much less mo tality SCHAUTA did not feel satisfied. It seemed to be cogent for a sur eon who did not close his eyes to the outstanding accomplishment of rad tion to try to improve the results of his surgery by utilizing radiatio for his operated cases. The so called »combination treatment» has bee tried first with roentgen by CLEVELAND and CLARK in the U. S. A., by)ESSAUER, GAUSS and SKINNER in Germany. The author was the first wh used radium for postradiation. We could indeed raise the percentage of f ve-year salvages just a little from 20 to 22 %. Further improvement coul l not be achieved because in our first attempts with radium treatmen it was not possible to destroy cancer cells remaining in the distant parts of the parametrium. In trying several methods of combining surgery with radiation we had to gain experience and we learned the hard way how to use efficient radiation on operated cases.

The author started first to insert a radium carrier with 40—50 mg element into the stump of the vagina for 10—12 hours four weeks after the operation and repeated the treatment five times at intervals of four weeks. We used this I. method in 44 cases. We could indeed improve our results: the relative 5- and 6-year salvages of the operated patients increased from 42 % without prophylactic radiation to about 55 % with radiation, but we had to pay for the improvement with a number of severe necroses and 8 recto- and vesico vaginal fistulae. Some patients even died from the effects of radiation while the autopsy showed that no cancer was left in the pelvis. We had been successful in destroying cancer but some patients had to pay with their lives.

It was first incomprehensible why fistulae and necroses should develop using a dosage which was always held below the lethal dosis for normal tissues which we had experimentally determined. The explanation was found in the changed local conditions after the extirpation of the uterus: the radium carrier had to be placed too close to the radio-sensitive mucosa of the bladder and the rectum. In using much larger doses in not operated cases we hardly ever saw fistulae because the cervix and the tumor were keeping the sensitive mucous membranes in a distance of $1^1/_2$—3 cm from the radium carrier. At the operation the muscularis of both organs was sometimes partly removed and frequently damaged and the protecting cervix was removed. Thus the radium came in close contact with the mucosae and the highly sensitive granulation tissue or the badly nourished scar tissue.

Considering the change in the local conditions our method was changed by reducing the dosage. In our II. method we inserted only 25—30 mg into the vagina for not more than 6 hours (65 cases). No fistulae developed,

but the permanent salvages were hardly better than they had been in the cases who had no radiation at all. Obviously, the smaller doses of radium applied in our II. method were not sufficient to destroy cancer cells left in the parametrium.

Our problem was: to apply a dose of radium sufficient to destroy cancer at the crucial point of attack, the pelvic wall without injuring highly sensitive tissues. There was not enough radium at our disposal to destroy cancer cells in distant parts of the parametrium — as HEYMAN does with his Teleradiation. It seemed too risky to insert interstitial needles. Furthermore we could not get a powerful roentgen machine — it was during World War I. We were in despair and we even thought we might have to give up postoperative use of radium. It was sheer accident and a piece of luck which finally brought the solution of our problem. At the regular control of cancer patients it happened that the author saw within one week two patients on whom he had performed an extended vaginal operation on two subsequent days more than three years ago. Both cases had been very progressed as the cancer reached deep in the parametrium which forced me to painstaking sharp dissection in order to release the ureter embedded in the carcinoma. After ligating the uterine vessels and freeing the ureter I found that the infiltration extended on the left side so deep into the parametrium that in order to finish the operation the parametrium had to be cut amidst the cancerous mass. I could see and feel with my fingers that carcinoma was left. The idea occurred to me then, to insert a radium carrier into the neoplastic tissue, what I did after closing the peritoneum in the routine method. I packed the wound with gauze. After 12 hours the radium was removed. Practically the same thing happened in the second case on the following day. Both patients recovered and could leave the hospital after two or three weeks. In both cases the microscopical examination proved that the whole parametrium was infiltrated with cancer and that the edge of dissection was in cancerous tissue. I was almost certain that both women would soon develop local recurrence in the parametrium and considered them dead, as they did not appear at the regular control of our cancer patients for several years. Of course I was more than surprised and very happy to see both women again after more than three years in the same week, not only alive but apparently in good health and without any sign of recurrence. They explained that they had not been able to come to Vienna during the war and, as a matter of fact, we have lost track of them again owing to the war and post-war conditions in Austria. In our statistics they are not counted as salvages but as dead from cancer, like all patients of whom we lost track and who had not been examined after five years. But if they are lost for the statistics these two cases initiated

the II. method of prophylactic radiation, the insertion of radium into the parametrium during the operation, which the author has been using since in 209 cases.

The author's routine method in operable cases of cervical cancer is a modification of Schauta's extended vaginal operation as described in 1928 at the British Obstetrical Congress in Dublin and demonstrated in a moving picture in 1931 at the meeting of the American Association of Gynecologists, Obstetricians and Abdominal Surgeons, in White Sulphur Springs and in 1938 at the meeting of the American Gynecological Society in Ashville, N. C. We make a paravaginal (SCHUCHARDT) incision on the side where there is more infiltration of the parametrium. After cutting the rectum pillars and sharp dissection of rectum and bladder, the ureters are freed by sharp dissection and the uterine arteries are ligated where they arise from the hypogastric artery. The Douglas is opened and the uterosacral ligaments and the lateral parametria are cut at the pelvic wall. Then only the anterior plica is opened and the uterus is extirpated with the adnexa after ligating the infundibulo-pelvic ligaments. As this part of the operation can be performed in less than 5 minutes the peritoneal cavity is open for a very short time only. After closing the peritoneum, a carrier with 50 mg of radium element screened in $1^1/_2$ mm brass is inserted in each of the parametric cavities at the pelvic wall. The radium carriers are kept in place by packing the cavity with sterile gauze which at the same time protects ureters, bladder and rectum keeping them in safe distance from the carriers. In cases where we were not certain whether the operation was really radical, a third and sometimes a fourth radium carrier was inserted and the carriers remained there between 8 and 12 hours.[1] It was gratifying that the recovery in these cases was smooth except for a few cases where the temperature rose up to 103° for a few days. The prophylactic radium application is followed by roentgen radiation starting 8—10 days after the operation (usually three series at intervals of 3—6 months). These roentgen radiations applying the full dosis cover the whole abdomen and pelvis. They intend to take care of cancer cells left in the pelvis and also of carcinomatous glands. Furthermore, beginning two months after the operation the author performs 5 prophylactic crossfire radiations at intervals of four weeks placing a special well screened radium applicator with 30 mg into the rectum at a distance of $1^1/_2$ cm from the mucosa and a second carrier with 30 mg into the vaginal stump. Both remain there for not more than 6 hours. We are not positive whether the cross fire treatment is necessary, but we can fairly assume that they prevent local recurrence in or behind the scar in the vagina which we had seen in a number of cases before using prophylactic radiation. Never having seen any unto-

[1] A description of the operation with illustrations of the technique is found in PACK and LIVINGSTON's excellent monograph on cancer treatment (P. HOEBER 1940).

ward effects or any damage we adhere to the method and the results have been very encouraging. In comparing the temporary salvage of operated patients treated by our III. method with the results in cases without radiation we saw an increase in cures from 72 % to 92.8 % after two years, from 60.9 % to 72 % after three years. What is really important in determining the value of our method is the permanent salvage which rose from 42 % to 58.8 %. The percentage of absolute salvages achieved with this combination of operation and radiation amounts to 32 %.

This compares favorably to the 20 % salvaged by vaginal operation or by laparotomy without radiation.[1] Therefore it was natural that the extended vaginal operation with immediate insertion of radium should be our method of choice for operable cases.

It was unquestionable that all inoperable cases should be treated with radiation. Having failed in being more radical it seemed logical that not only all cases of group 4 but many of group 3 should not be operated but radiated only. Furthermore, it seemed obvious that bad surgical risks should be excluded from operation although our vaginal operation had a very low mortality (3.9 % in the last 750 cases which is practically not more than the death rate after radiation. But in cases of group II and in some cases of group III we were faced with a problem because it was hard to decide especially in a number of borderline cases whether to operate or to radiate. It occurred to the author that the examination of the histological characteristics of different tumors should be helpful in the decision whether to operate or to use radiation in an individual case.

The Bergonié-Tribondeau Law states that immature cells and cells in an active state of division are more sensitive to radiation than cells that have already acquired their fixed morphological and physiological characteristics. This statement which also applies to radium rays explains why tumor cells are more radio-sensitive than normal tissue cells. It gives in a few words the biological basis for the so called »selective» effect of radium therapy, *i. e.* tumor cells which are highly reproductive but less differentiated in function and morphology are more radio-sensitive than normal tissue cells, epithelial cells are more sensitive than fibrous tissue.

In a study of 190 cases (2) we tried to find out which tumors were the most radio-sensitive. We classified the tumor cells after the procedure of Borst, Bard, Fabre, Schottlaender into mature, medium mature and immature cells.

[1] The figures differ from Peham-Amreichs for the following reason. Amreich's figures of my 3rd method include only 80 cases operated in the I. Frauenklinik till 1919, while the authors include all his cases operated till 1933 in the other hospitals (209).

According to the general rule immature cells are easier destroyed by radiation and the radio-sensitivity decreases with the higher differentiation of cells. We had expected that radiation of cancers with immature cells would give the best results. But it proved that this rule could not be applied to cervical cancer. On the contrary, cancer with higher maturity of cells seemed to respond better to radiation than carcinoma of the immature form. This paradox can be explained by the fact that the greater sensitivity of the unripe type is more than counterbalanced by the greater malignancy of its immature cells which tend to penetrate into the lymphatics of the adjacent tissues and to develop early metastasis. In addition to the differentation of cells other factors determine the radio-sensitivity of cancers. Exophytic tumors and tumors with little connective tissue were more radio-sensitive than craters. Furthermore tumors with lymphatic propagation and a good supply of blood and lymph vessels did not respond well to radiation. Since our first paper many authors have studied that problem and have come to different results, some confirming our investigations, some contradicting them. DOEDERLEIN and PHILIPP found no relation between cell grade and radio-sensitivity. MARTZLOFF (3) thinks that the spindle cell group of epidermoid cancer has a high degree of curability. The fat spindle type of MARTZLOFF corresponds to type 4 of BRODERS and to the anaplastic cells of HEALY and CUTLER. GLÜCKSMANN and SPEAR (4) found response of anaplastic tumor cells less satisfactory than that of differentiated tumor cells. WEAVER (5) says that among other factors the cell classification is important for the choice of treatment and prognosis. NORRIS and KIMBOROUGH state that the five-year salvage is greater in tumors with ripe cells than with unripe cells. SCHMITZ (6) says the cell type of cancer does not alter his plan of treatment which is 99 % radiation. MORTON (7) states the histologic type is of no value in prognosis. However, after having studied carefully the cell classification of cervical cancer in more than 500 cases our opinion has not changed. There is one exception, *i. e.* the adeno-carcinoma of the cervix which is certainly the highest differentiated of all cervical cancers but does not respond to radiation,[1] contrary to the cancers of fundus which generally are very radio-sensitive. From the histological point it is our belief that 1) adeno-carcinoma of cervix which is radium resistant must be operated, 2) cancers with immature cells should preferably be operated on, furthermore we have observed that cancers with lymphatic propagation respond much less to radiation than the plexiforms.

In making the decision whether to radiate or to operate and what type of operation to perform, also the lesions due to operation and radia-

[1] This was confirmed later by REGAUD, WINTZ, LACASSAGNE and others.

tion have to be compared. It has always been admitted by laparotomists that the lesions to bladder, ureter and rectum are more frequent after laparotomy than after the vaginal operation. In our last 328 cases of extended vaginal operation we had the following lesions: four lesions of the bladder (two of them radiated before operation), four lesions of the ureter (one of them in a case which could not be operated radically, two in cases radiated before operation), four recto-vaginal fistulae (two of them radiated before the operation) *i. e.* an average of about 3.6 %. In radiation the incidence of complications of rectum and recto-vaginal fistulae is 5—7.9 % (BLACK and WAUGH). MEIGS mentions 12.3 % of ureter fistulae in his first 65 operations, while no ureteral fistulae developed in his cases later. Contrary to MEIGS in our material the larger percentage of lesions was found in cases which had radiation before operation. Among our last 200 operations such lesions developed only in preradiated cases.

This fact should be considered in the highly important question whether radiation should be done before or after operation. Some authors believe that preradiation makes the operation more dangerous and leads to the development of fistulae. In the author's cases it is possible that the lesions of ureter, bladder and rectum were due to the fact that he did not chose the right time for surgery. It may be that we operated in some cases too early, in others too late. Considering the fact that the majority of fistulae occurred in preradiated cases we never used preradiation as a routine.

HEYMAN (8) who is the authority on radiation of uterine cancer »after studying the matter for many years on a material of over 1,000 cases» states »that a number of patients primarily healed by radiation therapy will probably be saved by operation from developing local recurrence, but a corresponding number of those who would have been definitely cured by radium therapy alone will succumb to the operation.» Therefore he comes to the conclusion that routine hysterectomy following radium therapy in cancer colli uteri is a dangerous experiment.

Also our experience gained in the course of years taught us that preradiation with both radium and roentgen with subsequent operation should not be used in all cases, but in selected cases only. Preradiation should be used 1) in all cases with infected and necrotic tumors or craters with foul putrid discharge because immediate operation could certainly endanger the patient's life, 2) in some cases which seem to be inoperable as the parametria are infiltrated to the pelvic wall. The striking recession of such infiltrations after relatively small doses of radium or roentgen indicates that the infiltrations were not cancerous but inflammatory. For such cases we are definitely in favor of tentative radiation followed by operation if the case becomes operable. However, the

radium dose should not be a very high one. In general, we agree with HEYMAN's statement that routine hysterectomy should not be performed after radium therapy because of its dangers. The time factor also seems to be of importance. About 6 weeks after the radium treatment is in our opinion a favorable time to operate because later on scar tissue may lead to difficulties in dissection and to lesions of bladder, rectum and ureters.

It is strange that the side effects and complications after radiation should have been disregarded or underestimated although they are not too rare. A reason for that may be that some of the sequelae occur very late, sometimes many years after radiation. MEIGS found 46 cases of serious bowel injury in his clinics and PHANEUF mentions delayed complications from radiation as one of the reasons for turning back to surgery.

CUTLER (9) states that activation of latent hemolytic streptococci is a real danger and is associated with 1—2 % mortality. ALDRIDGE (10) maintains sufficient radiation of uterine cancer cannot be applied without some damage to the intestinal tracts of many patients. In some cases palliative therapy will cure the irradiation injuries whereas in others operative interference is necessary.

After the observation of possibly 2,000 cases of cancer of the cervix, MEIGS »came to the conclusion that radiation is not the ideal method of treatment. Morbidity caused by the treatment in a large group of patients is great and depressing. The larger the experience with radiation and the longer the follow up of cases, the more discouraged has our staff become of our results. Radiation is not simple, we know how miserable patients are after roentgen and radium.» It is noteworthy that a man with his experience should feel prompted to make such a statement. One is inclined to think that perhaps the French method of radiation with massive doses which with some modifications seems to be accepted in U. S. A. may be responsible for the damage and the sufferings of the patients, facts which are but rarely mentioned in statistics. But there is another reason for it. Many men seeing only the striking primary results, the disappearing of bleeding and foul discharge but not the late complication think radiation technique is simple. Therefore their method of treatment is uniform in most cases. But radiation cannot be typified. There does not exist a »cancer dose» but the technique and dosage must be adapted to the special conditions of the individual case. This is what HEYMAN does. But only very few men have the experience, the skill and the humanity of a HEYMAN who has not to complain of the terrible sequelae after radiation. As a matter of fact, he hardly sees any fistulae using his individualistic method of treatment.

The author also had to deplore severe damage in the first years of radium treatment when he used the massive doses first advised by DOEDERLEIN, BUMM et al. For this reason we abandoned the treatment in one massive dose and instituted a modification of HEYMAN's method the so-called intermittent radiation where the patients do not suffer much from the treatment and its side effects (11).

In spite of the severe, sometimes incurable sequelae of radiation and the fact that many gynecologists think that cancer in lymphatic glands cannot be influenced by radiation ALLEN (12) reviewing 323 articles on the treatment of cancer of the cervix stated that 99 % of the authors of these articles, largely gynecologists and surgeons, regard irradiation therapy as the best method of treating cervical carcinoma.

JONES (13) comes to the conclusion that irradiation is the treatment of choice for the average cervix carcinoma and panhysterectomy is an unsatisfactory method of therapy for early cases. SCHEFFEY and HAHN (14) believe carcinoma of the cervix uteri is best treated by radiation alone. They admit that certain patients, carefully selected may have a better chance when treated surgically by one experienced in the rigorous technique of the radical operation preceded by irradiation, but in general this is not true. D. G. MORTON (15) states that approximately 90 % of cervical cancers are best treated by combination of radium and roentgen. Small proportions of patients, if carefully selected, are well treated by the WERTHEIM operation. 1943, GREENHILL (16) wrote »with few exceptions most gynecologists agree that irradiation is the treatment of choice in carcinoma of the cervix regardless of whether the cancer is early or advanced. The only exception is perhaps the case in which the cancer is so early that the diagnosis of malignancy can be made only by biopsy or the Schiller test. In such cases irradiation should follow complete hysterectomy.«

The few exceptions mentioned by GREENHILL were LYNCH and TAUSSIG, BONNEY, ADLER who was followed later by SUBOTH MITRA in India, ROSNER, SELLHEIM, KNAUS, KNAUER and STOECKEL in Europe. The latter has given the subject so much propaganda that the Schauta operation in Germany has been given the name of STOECKEL who added nothing but a little modification (2. Hilfsschnitt) which in our opinion is unnecessary in most cases.

In 1946 GREENHILL (17) states that in the U. S. A. and elsewhere most cases of cancer of the cervix regardless of whether they are group 1, 2, 3 or 4 are treated by radium and roentgen therapy. However, during the last few years there has been a decided trend toward operation in operable cases.

BAINBRIDGE (18) thinks that the one treatment of uterine cancer that has stood the test of time is surgery. Radiation or other treatment

should be used only as adjuvant following surgery and never in place of surgery except in utterly hopeless cases.

FERRIS (19) thinks a stage 1 of cervical epithelioma is best treated with radical hysterectomy followed by effective radiation. The prospect of cure of adeno-carcinoma of cervical canal is better by surgery.

MUELLER (20) states that most cases in his grade 0 and all cases in his grade 1 with small tumors are operated (operation is followed by irradiation). More progressed cases are irradiated and possibly subjected to secondary extirpation.

WERNER (21) gives only primary mortality, no permanent results of laparotomy. He also uses post-operative irradiation.

MARTZLOFF (22) comes to the conclusion that in order to obtain the best results from treatment with our present methods both radiology and surgery properly utilized offer a better outlook than one method singly employed.

ANSPACH (23) concludes his interesting article »Review of Problems of Cancer» with the words »perhaps a combination of irradiation and operation will improve results.»

This procedure has been advised by the author and his permanent results have been published in 1920, 1929, 1931, 1937, 1938, 1940. He called it the elective method of treating cervical cancer and the method was described as follows: 1) operation is performed in every operable case unless there exists a contraindication against operation (poor risk) or unless the patient refuses operation. 2) The method of choice is the vaginal radical operation performed under local anesthesia in twilight sleep (Dilaudid, Scopolamine). Mortality in 1,225 cases was 5.7 %, in the last 750 cases 3.9 %. Laparotomy being the more dangerous operation is performed only when there is a contraindication against vaginal operation. (Contracted pelvis, large fibroid, large inflammatory tumors with adhesions etc.) 3) The last step of the operation (described in detail on p. 481) is the insertion of two carriers of 50 mg radium into the wound at the pelvic wall for 8—12 hours. This is done in vaginal operation after closing the peritoneum, in laparotomy before closing it. Roentgen treatment beginning about 10 days after the operation and prophylactic radium treatment is performed in every operated case. 4) All inoperable cases and the operable cases in which operation was not performed are treated with irradiation (generally the author's intermittent method, a modification of the Stockholm technique) and roentgen. In some cases preradiation with radium and roentgen is performed, especially in cases of doubtful operability. Operation is performed if such cases become operable after the radiation. 5) The choice between operation and radiation is also influenced by the histological character of the tumor.

The author's statistics of the elective method show a five- or more

year salvage in 129 of 322 cases (39.4 %). Of the 129 cases the treatment has been combined vaginal extirpation and radiation in 106 cases (82.2 %), combined Wertheim operation and radiation in 4 cases (3.1 %), radiation only in 19 cases (14.7 %).

It is noteworthy that among the 106 cases of permanent cure by vaginal operation there were no less than 25 cases where the microscopical examination of the extirpated uterus and parametria showed that the operation had not been radical. In spite of that 9 of these 25 patients were alive and apparently free from cancer after five years. They would certainly have been lost without post-radiation.

Next to the old pioneers of surgery like VICTOR BONNEY, FRANK W. LYNCH and FRED TAUSSIG, it is especially JOE VINCENT MEIGS to whom we owe gratitude for the fact that also in U. S. A. the pendulum definitely swings again towards the revival of surgery. After finding poor results in early cases and being discouraged because patients who he thought should get well, did not, MEIGS became interested in the application of radical surgery to certain types of cervical cancer. He mentions especially that it has been shown that certain tumors are radiation resistant and thus incurable by radiation. The radium resistance of some cancers was one of our reasons not to give up surgery. MEIGS' operation is a combination of the WERTHEIM hysterectomy and TAUSSIG's node dissection. It is a »long, tedious and painstaking operation but one fairly easily accomplished by an experienced surgeon». MEIGS has operated on 100 selected cases without primary mortality, an achievement which nobody else has attained yet. Like in every new operation the number of secondary lesions was high. He had 12.3 % of ureter fistulae in his first 65 cases, but none within the last years owing to the better recognition of the blood supply of the ureter. If these excellent results can be maintained and if his permanent cures will be better than the absolute salvages of radiation and combination treatment, then MEIGS' operation will be the operation of the future for a limited number of cases in the hand of a skilled surgeon. Naturally such excellent results are only possible in selected cases. MEIGS for instance operates only 15 % of all cases while BONNEY and author have an operability of over 50 %. — MEIGS prefers to operate on patients under 50 years while there is no age limit for the extended vaginal operation. His unrivalled results were also made possible by the great progress in medicine, the sulfonamides, penicillin, the better preparation and the meticulous care of the patients, last but not least by his skillful surgery.

MEIGS believes that it is not possible to destroy with radiation cancer in lymph nodes. In this point the author does not agree with him, because as mentioned before, the increased number of salvages by the vaginal operation with post-radiation compared with the results of sur-

ger without radiation indicates that radiation can kill cancer in lymph nodes as well as in the parametrium. HEYMAN's results with teleradium for lymph nodes and cancer nests which cannot be reached with local radiation could hardly be explained otherwise. The 9 salvages mentioned before of 25 of our patients where the operation has not been radical seem to confirm this opinion. Microscopical examination of lymph nodes in patients who died after termination of the treatment should definitely answer this important question.

MEIGS' operation is selective and is not applied nor applicable to all cases. This statement cannot be emphasized too strongly. It is in accordance with the author's opinion: In treating cervical cancer one should not be dogmatic but the treatment has to be elective. The question should not be: radiation or surgery, but: which case is best treated by radiation, which by surgery and which by the combination of both. The choice of the operation will chiefly be influenced by the personal experience of the surgeon. If MEIGS' results can be matched by other gynecologists and if the permanent absolute cures will match or surpass the results obtained by our combined treatment, then MEIGS' operation certainly deserves a prominent rôle in the treatment of cervical cancer.

But we must admit that our present methods of treatment, surgery and radiation are not causal but local methods only. — While for a long time cancer was thought to be a local disease, to-day quite a number of scientists do not consider cancer a local but a general disease of the organism, caused by an anomaly of the metabolism or another unknown endogenous factor of constitutional nature. That readiness of the organism for developing cancer results in local manifestations caused by irritations of the tissues. Concerning cervical cancer, chronic inflammatory lesions are said to constitute the type of irritation which stimulates the local outbreak or overgrowth called cancer. Also incitation of local cancer of the sexual organs under the influence of sex hormones has been widely discussed. In rodents cervical cancer is developing after enormous doses of œstrogen. In women there is no proof that the same thing takes place. But all these stimuli could not produce cancer without a genetic predisposition of the individual. Therefore, for a long time already one has tried to strengthen the resistance of the body. Many scientists have been working without success on that problem. Lately, some authors have come to the conclusion that the defense mechanisms of the body are concentrated in the reticulo-endothelial system and the spleen. BRAUNSTEIN who has been working in the cancer institutions in Moscow, Berlin, and Institut de Radium Curie in Paris thinks that preparations of the spleen and the endothelial system can enhance the resistance of the organism and could thus exert a favorable action and help in combination with

surgery and radiation to check even advanced cases of cancer and to prevent recurrence after local treatment.

If cancer is really a general and not a local disease then the great progress in chemistry and atomic energy justifies the hope that science will also find a way to cure cervical cancer. But until this goal has been reached we must make the best use of our present methods. 1) Early diagnosis made possible by instruction of general practitioners, enlightenment of the lay-public and regular examination of healthy women. 2) Surgery must develop operations with low mortality which should not be too difficult technically. 3) In radiation the technique must be perfected and should not be schematic. In every case dosage and method of application should be adapted to the local conditions. The results of HEYMAN who emphasizes this method of treatment are steadily improving. 4) The method of cancer treatment with surgery and radiation should not be dogmatic but elective, surgery should as a rule be combined with radiation. 5) Prophylaxis of recurrence should be made effective by enhancing the defense mechanism of the organism and strengthening the patient's power of resistance.

Main Results

The dissatisfaction with the high mortality and with the poor permanent results of WERTHEIM's cancer operation prompted WICKHAM, DEGRAIS, DOEDERLEIN and KRÖNIG to give up operation for cervical cancer and to substitute it by radiation. The »treatment without operation» was accepted practically in the whole world and in the course of years could accomplish the same results as laparotomy with much lower mortality. But not more lives could be saved by radiation than by laparotomy. SCHAUTA in Vienna and his school did not give up surgery. They chose another way to reduce the death rate following operation and developed the extended vaginal operation which could in a series of more than 1,200 cases match the results of laparotomy with a much smaller mortality. The author modified SCHAUTA's operation and added immediate post-operative insertion of radium followed by roentgen radiation. He could improve the permanent results from 20 % to 32 %. HEYMAN's work in the Radiumhemmet is unrivalled. In more than 4,000 cases he had 28.8 % permanent cures, within the last 10 years 34.9 %.

Lately, in the countries which had given up operation there is a trend towards the revival of surgery. MEIGS performed a radical WERTHEIM operation plus lymphadenectomy in 100 cases without mortality. But only 10—15 % of all cases were considered eligible for MEIGS' operation.

The author has advised the »elective treatment» of cervical cancer which he used for more than 20 years. His method of choice is the extended vaginal operation with immediate insertion of radium. Laparotomy with radium insertion is performed in cases unfit for the vaginal operation and radiation in inoperable cases and bad surgical risks. The permanent cures with his elective method amount to 39.4 %. The primary mortality was 3.9 % within the last 15 years.

SUMMARY

After a survey of the history of surgery and radiotherapy in cervical cancer the author describes the »elective treatment» of this disease, which he used for more than 20 years: extended vaginal operation with immediate insertion of radium in most cases. Laparatomy with radium insertion is performed in cases unfit for the vaginal operation and radiation in inoperable cases and bad surgical risks. The permanent cures with this elective method amount to 39,4 %. The primary mortality was 3.9 % within the last 15 years.

ZUSAMMENFASSUNG

Nach einer Übersicht der Geschichte der Chirurgie und Radiotherapie des Kollumkrebses beschreibt Verf. die von ihm seit über 20 Jahren verwendete »Behandlung der Wahl» dieser Krankheit: ausgedehnte vaginale Operation mit unmittelbarem Einlegen von Radium in der Mehrzahl der Fälle. Laparotomie mit Einlegen von Radium wird bei für die vaginale Operation ungeeigneten Fällen vorgenommen und Bestrahlung bei inoperablen Fällen sowie bei grossen Operationsgefahren. Die Dauererfolge mit dieser Methode der Wahl betragen 39.4 %. Die primäre Sterblichkeit betrug in den letzten 15 Jahren 3.9 %.

RÉSUMÉ

Après un coup d'œil jeté sur l'histoire de la chirurgie et de la radiothérapie dans le cancer du col, l'auteur décrit le »traitement de choix» de cette affection, qu'il a employé pendant plus de 20 ans: opération vaginale large avec insertion de radium dans la plupart des cas; dans ceux où l'intervention par voie vaginale n'est pas applicable, laparotomie avec insertion de radium; et chez les sujets inopérables, ainsi que là où l'opération chirurgicale offre trop de risques, irradiation. Les guérisons durables par cette méthode de choix ascendent à 39.4 %. La mortalité primaire a été de 3.9 % au cours des dernières 15 années.

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FROM KING GUSTAF V's JUBILEE CLINIC (HEAD: BERTIL EBENIUS, M. D.) AND THE GYNAECOLOGICAL CLINIC (HEAD: ALF SJÖVALL, M. D.) OF THE UNIVERSITY OF LUND, SWEDEN

PARAMETRITIS AS THE FIRST AND ONLY SYMPTOM OF CERVICAL CARCINOMA DURING PREGNANCY[1]

by

Bertil Ebenius and *Alf Sjövall*

The common symptoms of cervical carcinoma, bleeding and discharge, are often misinterpreted during pregnancy as due to an imminent abortion, placenta praevia or a vaginal discharge of no importance. On the other hand there are cases of cervical carcinoma in pregnant women who are quite symptomfree.[2]

In a case of cervical carcinoma during pregnancy treated by the authors both bleeding and discharge were entirely absent but the presence of a parametric inflammatory swelling eventually led to the detection of an early neoplasm of the portio. In the available literature no similar case was found. The history of our patient which is of some diagnostic interest is as follows.

On January 22, 1945, Mrs. J., 35 years old, was admitted to the Gynaecological Clinic on account of abdominal pains and fever. She was pregnant and her last period had been on the 25th of June 1944. She had been married in 1932. After several early and late abortions she had had normal deliveries in 1937 and 1940 with healthy children. Her Wassermann reaction was negative.

Two and a half months prior to admission she had suffered from attacks of right-sided abdominal pains, fever and chills. They had been treated as due to pyelitis by her family physician.

On the last four days before admission there had been severe pains in the right flank irradiating to the right side of her back. On the last day there had been fever too, but no other symptoms of any kind.

[1] Submitted for publication, May 23, 1947.

[2] for instance:
CLAVE, A. M. J. Obst. 41: 404, 1934.
WOLFEBAEK, F. Med. Rev. 35: 353, 1935.
RICHMANN, S., and GOODFRIEND, M. J. Am. J. Roentgenol. 48: 677, 1942.

Besides a pregnancy in the eighth month, *examination* revealed considerable tenderness in the lower abdomen on the right side of the uterus, without muscular defence or rigidity. No swelling could be felt from above. The rectal temperature was 38.6° C. Microscopical examination showed that the urine was normal. An appendicitis abscess or a necrotic myoma were considered as the diagnostic possibilities. After only a few days of rest in bed there was a marked improvement in her condition and the temperature became normal. About a week later she caught a fever again, remittent by about 38° C. for 3 weeks, without any other change in her condition. A right-sided, tender, hard parametric swelling as large as an orange, adhering both to the uterus and to the pelvic wall, could now be felt on vaginal examination. The swelling had all the characteristics of a usual parametritis, affecting the right sacro-uterine and cardinal ligaments low in the pelvis and did not resemble an appendicitis abscess or an infected neoplasm at all. *The cervix was normal to the feel.*

During the entire course of the illness there had been no bleeding and no vaginal discharge.

The cause of the inflammatory parametric swelling seemed enigmatical. Nothing had been done by the patient to provoke an abortion. Both she and her husband desired the child. The possibility of cervical carcinoma was of course discussed but seemed too far-fetched as there had been no vaginal bleeding or discharge and as the cervix was entirely normal on palpation.

After the examination the temperature went up to 39° C. and a chill set in. Blood culture was negative. The fever responded to sulphatiazole $4 + 4 + 1\ g \times 6$.

As the inflammatory process evidently could not be supposed to be sufficiently quiet at term — the pregnancy was now so far advanced that the child could be expected to be well viable — we did not dare to let her go into labour. Hence a caesarean section was considered the least dangerous way of delivery. At the operation a more precise diagnosis of the swelling could be obtained as well.

The operation was done in spinal percain anesthesia as an isthmico-corporeal longitudinal incision. The child was healthy and weighed 2,600 g. There was a hard infiltration of the right broad ligament and parametrium almost as large as an orange. The right Fallopian tube showed a slight redness and there was a slight fibrinous exudation on the serosal covering of the right broad ligament, otherwise everything was normal. The uterine wound was sutured in the usual way and was entirely covered with the vesicouterine fold. The abdomen was closed.

The diagnosis parametritis had thus been verified. *In spite of the absence of other symptoms the only possible cause seemed to be a carcinoma of the cervix.* On account of that a biopsy was made from the posterior

lip of the portio which showed a lesion looking like a usual innocent papillary pseudoerosion as large as a halfpenny piece.

Microscopical examination revealed growth of atypical epithelial cells with abundant mitoses in a tissue with marked inflammatory reaction. In some places there was a suspicion of invasive growth. The finding was characterized as looking suspiciously like something of carcinomatous nature (Prof. AHLSTRÖM).

The biopsy was followed by a chill and fever, 40° C. The swelling grew more and more tender and 4 weeks later it was considered necessary to drain the parametritis to get the patient into a better condition and make her fit for radiological treatment.

A cross incision above the right inguinal ligament was made in local infiltration anesthesia and ether narcosis. The iliac vessels were imbedded in a hard infiltration and at the centre of the parametrium there was a little abscess as large as a hazel-nut. A tubing drain was introduced. A lymph node and a piece of the parametric tissue were microscopically examined. They showed only inflammatory infiltration but no carcinoma. Bacterial culture from the abscess gave growth of γ-streptococci.

About a fortnight later, when the patient had improved, 4 biopsies were made from the portio. The microscopical diagnosis of undifferentiated squamous cell carcinoma was now established.

During the uneventful healing of the parametritis the patient was transferred to the Jubilee Clinic for irradiation on the usual lines. The case was classified as belonging to stage II, the tumor affecting a little part of the posterior fornix.

Radiotherapy was started with a combined intrauterine and vaginal radium application. One week later a second application of the same kind was given. On each irradiation the intrauterine dose was 990 mgh. and the vaginal between 1,500 and 1,600 mgh. The third combined application, given after an interval of three weeks, had to be interrupted as the patient caught a fever of about 39° C. It was, however, possible to continue the irradiation five days later when the temperature was normal again. The intrauterine and vaginal dose was about the same as before.

Roentgen treatment against the parametria was given in connection with the first radium application and she got 1,500 and 1,000 r respectively on the skin on each of two anterior and two posterior fields.

The aftercourse was uneventful, and the tumour as well as the parametric infiltration disappeared completely. At the last examination on April 24, 1947, more than two years after the treatment, the patient was in good condition without any signs or symptoms of recurrence, and her child was well too.

SUMMARY

The clinical course of a case of carcinoma of the cervix uteri during pregnancy is described on account of its interest from the diagnostic point of view. The patient was admitted with an inflammatory parametric swelling. She was in the eighth month of her pregnancy. There had been no bleeding and no vaginal discharge at all. The cervix was normal to the feel. After performance of a caesarean section when the child had become well viable, repeated biopsies from the portio were made as a carcinoma seemed to be the only reasonable cause of the parametritis. The portio showed a lesion looking like a usual innocent pseudoerosion. The second biopsy yielded conclusive evidence of malignancy, showing a squamous cell carcinoma. After incision and drainage of the parametritis from above radium and roentgen treatment was performed along the usual lines. More than two years after treatment the patient is still healed, and her child is well.

ZUSAMMENFASSUNG

Der klinische Verlauf eines Falles von Krebs des Cervix uteri in der Schwangerschaft wird wegen seines diagnostischen Interesses beschrieben. Die Kranke wurde mit einer entzündlichen Schwellung des Parametriums aufgenommen. Sie war im achten Schwangerschaftsmonate. Blutungen oder überhaupt vaginaler Ausfluss waren nicht vorgekommen. Der Tastbefund des Zervix war normal. Nach Vornahme eines Kaiserschnitts, als das Kind gut lebensfähig geworden war, wurden wiederholt Probeexzisionen aus der Portio gemacht, da ein Krebs die einzig denkbare Ursache der Parametritis zu sein schien. Die Portio zeigte eine Läsion vom Aussehen einer gewöhnlichen, ungefährlichen Pseudoerosion. Die zweite Probeexzision ergab den Beweis der Malignität, indem sie einen Plattenepithelkrebs nachwies. Nach Inzision und Drainierung der Parametritis von oben her wurde nach den gewöhnlichen Prinzipien Radium- und Röntgenbehandlung gegeben. Mehr als zwei Jahre nach der Behandlung ist die Patientin noch immer gesund, und ihrem Kinde geht es gut.

RÉSUMÉ

Communication, justifiée par son intérêt diagnostique, de l'évolution clinique d'un cas de cancer du col pendant la grossesse. La malade, enceinte du huitième mois, fut hospitalisée pour paramétrite. Pendant sa grossesse elle n'avait eu ni hémorragie ni pertes blanches.

Attendu qu'un cancer du col apparaissait comme la seule cause plausible de la paramétrite, on pratique — après césarienne, l'enfant étant devenu viable — des biopsies répétées de la portio, qui ne montra que des altérations semblables à celles d'une pseudo-érosion commune et bénigne. Cependant la seconde biopsie mit en évidence un carcinome pavimenteux. Après incision et drainage de la paramétrite par le haut, la malade fut soumise à un traitement par le radium et les Rayons Roentgen. Au bout de plus de deux ans la patiente est en bonne santé et ne présente aucun symptôme pathologique. Son enfant est vivant et bien portant.

FROM THE ROTTERDAMSCH RADIOTHERAPEUTISCH INSTITUUT, ROTTERDAM, HOLLAND
(DIRECTOR: D. DEN HOED)

METHODS TO REDUCE THE DANGERS OF RADIOTHERAPY IN CANCER OF THE UTERUS[1]

by

D. Den Hoed

The goal of the life of Prof. J. HEYMAN has been to further radiotherapy in gynecology and thanks to his remarkable work in this domain the methods of Stockholm are accepted far over the world and have been a stimulus for many researchers.

One of the chief advantages of radiotherapy in cancer of the cervix uteri over the surgical methods is the much smaller danger in radiological treatment and in most statistics on carcinoma cervicis uteri the primary mortality is stated as only 2 to 4 %.

One of the causes of primary mortality in radiotherapy is due to infection leading to sepsis or peritonitis.

Table I.

Mortality due to infection in radiotherapy of carcinoma of the cervix (according to DUCUING).

SCHRÖDER	2.7	KEHRER	6.2
WAGNER	0.3	REGAUD	1.6
DÖDERLEIN	0.7	HEYMAN	2.0
Centre anticancéreux Toulouse	3.7	DUCUING	2.8

As the radiotherapeutical methods are more or less standardized — one of the standard methods being the Stockholm treatment — in future one cannot expect much better results in the different stages of the disease. Improvement in our total cure rate has to be found by trying to treat patients in an earlier stage; this can only be achieved by collaboration of general practitioners, gynecologists, radiotherapists and last but not least by education of the public to seek advice earlier. Up till now we are obliged to treat the patients as they are sent to us, most of them

[1] Submitted for publication May 14, 1947.

being in an advanced and even in a far advanced stage. Therefore we have to try to ameliorate our results by technical improvements.

As quoted before the primary mortality is mostly stated as a small percentage and searching for the causes of this mortality and learning to avoid these sources of failure will help to improve our results.

In cancer of the uterus numerous complications may arise spontaneously. It is mostly not the carcinoma itself which is the direct cause of death in this affection, but one of the complications such as hemorrhage, phlebitis, thrombosis, embolism, infection of the urinary passages, uraemia, infection of the pelvic tissue, septicopyaemie, bronchopneumonia and the like, while suffering is often increased by the appearance of rectovaginal or vesicovaginal fistulas. Therefore it is no wonder that when patients, suffering from carcinoma cervicis uteri and especially those who are in an advanced stage, are treated, serious complications often supervene, in which it is however sometimes difficult to say or improbable that they are the *results* of treatment (*i. e.* hemorrhage, thrombosis, embolism); on the other hand some of the complications are decidedly due to or aggravated by the treatment.

In the first place I wish to devote attention to the chance of infection in radiotherapy of cancer of the cervix.

Cancer of the cervix usually shows ulceration, in which, as a rule pathogenic germs are present. The chance of infectious complications in consequence of irradiation is increased by the manipulations in applying radium and by the decrease of the local resistance to inflammation due to high doses of radiation necessary to damage the cancer-cells. It is a wellknown fact that heavily irradiated tissue is very sensitive to infection!

Besides it can be proved that the chance of infection depends on the nature of the germs and the general resistance of the patient against her own vaginal flora, the relation of which may be established by the test of Ruge-Philip. This test is executed in the following manner[1]: By venepunction 10 to 20 cc of blood are taken under sterile conditions, after defibrination with small glass balls this is infected with a small drop of the secretion of the ulcer at the cervix. After thorough mixing an agar disk is cast with 1 cc of this mixture and placed in an incubator at 37° C. as is the rest of the blood secretion mixture.

After one, two and three hours other disks are cast, always taking the same quantity of agar and of infected blood. After 24 hours the result of the incubation is controlled. From the first disk we get an impression of the sort and the number of the germs present in the ulcer and from the following plates we learn the strength of the bactericidal power of the

[1] Dr. WATERMAN (Amsterdam) has been so kind as to do most of the bacteriological work.

blood of the patient against her own vaginal flora. This cultivation method is more or less selective as chiefly only pathogenetic germs thrive in this milieu.

The presence of haemolytic streptococci and the absence of bactericidal power proved both of serious prognostic significance.

Taking these factors into consideration we can distinguish four combinations.

By 500 patients tested in this way the various combinations turned out to occur in the following proportions.

Table II.

	Group I	Group II	Group III	Group IV
Percentage of cases	55 %	20 %	7 %	18 %
Bactericidal power	+	+	—	—
Haemolytic streptococci	—	+	—	+
Prognosis as to chance of infection	favourable	somewhat doubtful	doubtful	bad

It has appeared from our and other investigations that serious infectious complications mainly arrive in the highly threatened group IV as will be shown in the following tables.

Table III.

Results of Ruge-Philip test	Total number of applications	Reactions (1)				
		Unimportant			Serious	
		None	1 day	1—3 days	3—5 days	> 5 days or dead
Group I. Bactericidy present ..... No haemolytic streptococci..	740	391	225	82	17. 6 %	25
» II. Bactericidy present ..... Haemolytic streptococci present	245	104	84	32	14 10 %	11
» III. No bactericidy ..... No haemolytic streptococci..	95	39	27	16	10 14 %	3
» IV. No bactericidy ..... Haemolytic streptococci present	222	103	61	20	14 17 %	24
	1 302	637 48 %	397 31.1 %	150 12 %	55 4 %	63 5 %

Table IV.

	None	Slight		Serious		Number of appl.
		1 day	1—3 days	3—5 days	5 days or dead	
Reactions in 12 patients from group IV before the introduction of the method »Damme»	12 (32 %)	10 (26 %)	2 (5 %)	4 (11 %) (37 %)	10 (26 %) (2 †) (16 %)	38
Reactions in 63 patients from group IV after the introduction of method »Damme»	94 (48 %)	53 (27 %)	20 (10 %)	14 (7 %) (15 %)	16 (8 %) (1 †) (< 2 %)	197

Of a series of 300 patients the number of infection complications were exactly controlled in the various groups.

Since our method of treatment entails repeated applications of radium and moreover mostly two series of Röntgen rays the number of treatments each of which may induce complications is many times larger than the number of patients.

The reactions are distinguished as none, one day, one to three days, all of these considered as unimportant and serious reactions lasting 3 to 5 days, longer than 5 days or leading to death.

This classification is based on the following considerations.

A reaction of one day, usually only some tenths of a degree C° elevation of temperature, can hardly be taken as an effect of radiation. Some such reaction we may see after vaginal examination, slight constipation or tamponade.

A reaction of up to 3 days may still be called slight. Mostly there is no objective symptom but a moderate rise of temperature.

Reactions of from 3 to 5 days are a little more serious. Sometimes oedema of the vulva or pain by pressure on the parametria was found.

Reactions of longer duration are mostly due to a severe state of infection (perimetritis, parametritis, phlebitis, salpingitis, septico-pyaemy, local or generalised peritonitis.)

As stated above it is good luck that most of our patients belong to group I in which no dangerous germs are present, while the patients prove to possess bactericidal power against the germs present in their own ulceration. Less than 20 % were severely threatened by the presence of haemolytic streptococci, in particular since they showed a bad resistance (absence of bactericidal power) to their own flora. Nevertheless in all groups more or less severe reactions were seen but the relation

to our grouping is close enough, specially, as knowing the significance of the bacteriological examination, we treated the more threatened groups with greater caution than group I, so that we may assume that in doing so we prevented many dangerous reactions in group II, III and IV.

Table III clearly shows the connection between the nature and the number of complications and the immunological relations. The advantage of this bacteriological test is the fact that it gives a warning, when there is a great chance of serious complications and therefore one will be able to carry out therapy with more surety and safety.

If after application of radium we got a slight reaction our line of conduct was guided by the bacteriological findings. In patients belonging to group I we followed a wait and see policy, but in group II and III we were on the alert, while the irradiation of the patients from group IV immediately was interrupted and the treatment stopped till the temperature and the local and general conditions of the patient seemed to be normal again.

In acting in this manner most severe complications could be avoided. Still this method did not satisfy completely as it sometimes proved to be impossible to finish the intended treatment which resulted in missing the chance of curing a patient.

However in consequence of the elaborate study of DAMME from the school of Daels (Gaunt) it soon became apparent that the number of complications can be greatly diminished by applying a modified method of irradiation in group IV; before passing on to a heavy treatment a small quantity of radium (5 to 10 mg) was applied to the ulcer during a fairly long session (30—50 hours). After this preirradiation with low intensity and small total dose the heavy treatment could mostly be started with much less risk (Table IV).

Analyzing this empirical fact we found that in several cases a previously failing bactericidal power of the blood presented itself, which may be the explanation of this remarkable finding.

In the last series of some hundreds of cases treated along these rules the mortality due to local infection was only 0.3 %.

Owing to the war conditions in our country soon after 1940 I was obliged to stop the bacteriological examinations, This was followed by a slight statistically insignificant increase of severe infectious complications in radiological treatment of cancer cervicis uteri and even one death due to local infection occurred in a series of 103 patients.

Under the impression of these facts we introduced the treatment with sulfathiazol in this domains.

The intravaginal radium applicator was always introduced together with an intravaginal dose of sulfathiazol (or orgaseption) of 1 to 2 g. If intrauterine application, which as may be easily shown, is more often

followed by serious infections than intravaginal or external irradiation, was planned, 2—3 g of sulfathiazol are given intraoral 1 hour before the introduction of the radium and during the course of this treatment every four hour 1—2 g.

In table I we see that in a total number of 1,302 applications only 637 (48 %) did not show any reaction to radiation; in the following series we treated along this new principle, in 533 applications 351 sessions (65 %) were not followed by any reaction and in a number of 150 patients prophylactically treated with sulfathiazol no single death due to infection occurred.

It may be concluded from these facts that the prophylactic treatment with sulfathiazol in radiotherapy of the uterine cancer is an important improvement.

In some patients the tumour is intensely infected and consists partly of a large necrobiotic mass; in the clefts of the growth and in the interstitial tissue the microbes prosper and give rise, even spontaneously, to high temperature, bad general conditions and severe reactions.

In such cases treatment according to our rules is often impossible. In very exceptional cases of this kind we therefore resort to excochleation of the necrotic and necrobiotic parts of the tumour. After this auxillary treatment the infectious state of the growth and the patient is ameliorated and our usual radiotherapy is well tolerated.

A second important complication in the treatment of cancer cervicis uteri is the proctitis. This is a consequence of our heavy dosage which according to the statistics had yielded remarkably good rates of recovery, but has of course increased the chance of proctitis by irradiation.

However, we estimate the greater chance of recovery higher than the mostly temporary troubles due to proctitis, so that we only altered very gradually our method to avoid these complications as much as possible.

It is evident that this complication which in some severe cases leads to formation of rectovaginal fistulae, is not completely avoidable since in many patients the tumour infiltrated the backwall of the vagina and sometimes has penetrated into or close to the rectal mucosa. Therefore in order to obtain a cure in such patients one is obliged to irradiate with a heavy dosage the rectal mucosa as well, inevitably resulting in proctitis.

For the last 10 years however our mode of irradiation has been altered in order to spare the rectal mucosa as much as possible. To this purpose the intravaginal radium application was diminished from a total of 4,500 mg hr. Ra El. given in 2 sessions with an interval of one week to 4,000 mg hr. Ra El in 2 sessions. Besides we changed our external Röntgen irradiation in the following manner.

Formerly we applied 4 fields, one from the back, one from the front and one from each side.

These fields got 400 r per session, in total 800 to 1,200 r pro field.

During the last 10 years a lead strip of 4 cm was placed in the middle of the front and back field in order to spare the rectovaginal septum which is situated in the centre of the pelvis.

It is clear that large tumours will often displace the radium applicator in the direction of the rectovaginal septum and the vaginal vault is practically filled up with the mass of the growth. This prevents us from making a certain distance between applicator and rectovaginal wall by packing the vagina with gauze and enhances the chance of proctitis and formation of fistulas.

Therefore we often make use of Röntgen-contact-irradiation which method enables us to direct the beam away from the rectum. In this manner we succeed too in sloughing down the bulk of the tumour, whereupon the normal radium applicator may be installed with much less danger for the rectal mucosa.

A second advantage of this method is the fact that the bleeding from the tumour, which is often the cause of weakness of the patient and diminishing of the general resistance, is mostly stopped soon. Doses of 20,000 r or more to the surface of the tumour are not exceptional.

Indeed it has appeared to be possible to diminish the severe proctitis to a lower percentage.

In 380 old case histories about 50 % of proctitis was stated. In 17 % of the cases this affection was stated as serious, while 6 % of our patients showed sectovaginal fistula. In the last series of more than 200 patients only in 30 % proctitis was found; in 8 % of these patients the affection had to be classified as serious, which led in two cases only to fistulae (1 %). In one of these patients already before irradiation the tumour had penetrated through the rectal mucosa giving rise to ulceration in the rectum, a situation which is practically the beginning of the formation of a spontaneous rectovaginal fistula.

Table V.

Treatment	Slight proctitis	Severe proctitis	Rectovaginal fistula
Old method	33 %	17 %	6 %
	50 %		
New method	22 %	8 %	1 %
	30 %		

SUMMARY

The author has rather well overcome the dangers of the infectious complications. The importance of prophylactic treatment with sulfadrugs is stressed.

In very exceptional cases excochleation is recommended as an auxillary treatment. The injury of the rectum is not wholly avoidable but lowering of the intravaginal radium dose and application of a lead strip above the rectum in the back and front field of the Röntgen irradiation scheme have reduced this mischief to slight proportions. Sometimes contact-Röntgen-irradiation with a beam directed away from the rectum is used for bulky tumours. By thus sloughing down the bulk of the tumour more room is gained to introduce the radium applicator and the gauze tampon. In this manner the arising of rectovaginal fistulas due to irradiation has been practically totally avoided.

ZUSAMMENFASSUNG

Es ist Verf. gelungen, die Gefahren der infektiösen Komplikationen ziemlich gut zu beherrschen. Die Bedeutung prophylaktischer Behandlung mit Sulfadrogen wird betont. In sehr seltenen Fällen wird die Exkochleation als unterstützende Behandlung empfohlen. Die Schädigung durch die Rektumsbestrahlung lässt sich nicht ganz vermeiden, doch haben Herabsetzung der intravaginalen Radiumdosis und Auflegen eines Bleistreifens über das Rektum im Hinter- und Vorderfelde des Röntgenbestrahlungsschemas diesen Nachteil auf geringe Masse beschränkt. Manchmal wird bei umfangreicheren Tumoren Kontaktröntgenbestrahlung mit vom Rektum hinweggerichtetem Strahl ververwendet. Durch diese Verkleinerung des Tumors gewinnt man besseren Platz zum Einführen des Radiumapplikators und des Gazetampons. In dieser Weise hat man die Entstehung von durch Bestrahlung bedingten rektovaginalen Fisteln so gut wie völlig vermeiden können.

RÉSUMÉ

L'auteur a conjuré d'une façon plutôt satisfaisante le danger des complications infectieuses. Il souligne l'importance d'un traitement prophylactique par les sulfamides. Dans des cas très exceptionnels il recommande l'éxcochléation à titre de traitement adjuvant. Les lésions rectales dues à l'irradiation ne sont pas complètement évitables, mais cet accident a été réduit considérablement, en diminuant la dose intravaginale du radium et en appliquant une bande de plomb au-dessus du rectum, dans les champs postérieur et antérieur du schéma de l'irradiation par les rayons Roentgen. Parfois, pour les tumeurs plus volumineuses, on se sert de la radiothérapie de contact, avec un rayon s'écartant du rectum. En diminuant ainsi la tumeur on gagne de la place pour introduire l'applicateur portant le radium, et le tampon de gaze. De cette façon on a pratiquement tout à fait évité l'apparition de fistules recto-vaginales dues à l'irradiation.

FROM THE RADIUMCENTER IN ODENSE, DENMARK (CHIEF: P. JACOBY)

THE EXPERIENCES WITH RADIOTHERAPY IN CANCER OF THE CERVIX AND OF THE CORPUS OF THE UTERUS AT THE RADIUMCENTER IN ODENSE[1]

by

P. Jacoby

Those radiotherapeuts throughout the world and especially in Scandinavia who are interested in radiotherapy of the cancer of uterus are greatly indepted to professor HEYMAN on behalf of his huge and important work in this field of medicine. Dr. HEYMAN has made the foundation upon which radiotherapy of the cancer of uterus has been outlined at the Radiumcenter in Odense. By this publication about the results of radiotherapy of the cancer of the uterus from the Radiumcenter in Odense, I wish to express my gratitude to Dr. HEYMAN on his retirement from a long and splendid day of work.

Our material is relatively small compared with the large series of patients treated by Radiumhemmet in Stockholm, but after many years of work although sufficiently large to be included in the fifth volume of statements concerning radiotherapy of the cancer of uterine cervix formerly published by the health organisation of the league of nations and edited by Dr. HEYMAN.

The entire Material

The Radiumcenter in Odense is the smallest of the three centers in Denmark, and the number of patients visiting this center can only be expected to be one third of the patients coming to each of the other two centers in Copenhagen and Aarhus. The material for this publication is collected from July 1st 1928 until December 31st 1941, in which time the author has been head of the center. In 1928 only two beds were available, in 1929 six beds were at our disposition, but in 1931 the number of beds was increased to 28. A new Radiumcenter with in all 50 beds was opened in 1938 and at the same time a change was made in the staff.

[1] Submitted for publication, July 2, 1947.

In the first period until 1938 the responsibility for the radium treatment of the cancer of the uterus was that of Dr. SVEN MÜLLER, chief surgeon at the hospital and only the roentgen treatment was under the supervision of the radiological staff. From 1938 the whole responsibility for the treatment for as well radium as roentgen was in the hands of the radiological staff having Dr. POUL KUHNEL, chief gynecologist of the hospital as advisor in gynecology. Following this arrangement there has been a better opportunity to increase our experience both by a more careful follow-up and to make modifications in the treatment when this seemed profitable.

In the first period from 1928 to 1937 in all 1,747 new patients with malignant diseases were treated at the center. 215 of these patients had cancer of the cervix (12.4 %). In the second period from 1938 to 1941 in all 1,481 new patients with malignant diseases were examined of which 158 had cancer of the cervix (10.2 %); this makes a total of 373 patients having cancer of the cervix of the uterus. Besides 98 patients with cancer of the corpus of the uterus have been examined with the view to treatment in the whole period from 1928 to 1941.

Omitted from this material are all cases of cancer of the cervix or the corpus of the uterus having a coincident involvment of another organ of the genital tract. Besides all cases treated elsewhere have been excluded.

Cancer of the Cervix of the Uterus

The material

As mentioned above 373 patients were examined with a view to treatment, but only 365 were treated (including those incompletely treated).

Table I shows the *distribution in age-groups*. All ages from 20 to 80 are represented, and the disease seems to be most common in the fourth decade of life.

Table I.

All cases of cancer of the cervix divided according to age; each group representing 10 years.

Age	20—30	31—40	41—50	51—60	61—70	71—80	Total
Number of patients..	26	37	105	86	55	14	373
Percentage	7 %	24.1 %	28.1 %	23 %	14.6 %	3.2 %	100 %

Table II a shows the *distribution* of the material *into the four accepted stages of disease* (the definition accepted by the health organisation of the league of nations in 1937). The patients examined before 1937 have been regrouped according to the description in the files. The last three years represent a rather marked increase in the morbidity.

Table II a.

Evaluation of the results of treatment of all radiological treated cases of cancer of the cervix grouped according to the four stages.

	Stage I	Stage II	Stage I + II	Stage III	Stage IV	Stage III + IV	Total
Patients treated	87	109	196	113	56	169	365
Patients alive free of symptoms	60	42	102	14	4	18	120
5 years relative cure rate	69 %	38.6 %	52 %	13.4 %	7.1 %	10.7 %	32.9 %

Table II b.

Grouped in two periods 1928—1937 and 1938—1941.

	Stage I	Stage II	Stage I + II	Stage III	Stage IV	Stage III + IV	Total
				1928—37.			
Patients treated	40	66	106	80	25	105	211
Patients alive free of symptoms	26	24	50	4	1	5	55
5 years relative cure rate	65.3 %	26.4 %	47.2 %	5 %	4 %	4.5 %	26 %
				1938—41.			
Patients treated	47	43	90	33	31	64	154
Patients alive free of symptoms	34	18	52	10	3	13	65
5 years relative cure rate	72.2 %	41.6 %	57.8 %	30.2 %	9.7 %	20.3 %	42.2 %

Table II c.

Grouped in three periods 1928—33, 1934—38 and 1939—41.

	Stage I	Stage II	Stage I + II	Stage III	Stage IV	Stage III + IV	Total
				1928—33.			
Patients treated	18	44	62	45	12	67	119
Patients alive free of symptoms	11	15	26	1	1	2	28
5 years relative cure rate	61 %	34.2 %	41.8 %	2.2 %	8 %	3 %	23.4 %
				1934—38.			
Patients treated	32	28	60	43	18	61	121
Patients alive free of symptoms	24	10	34	6	0	6	40
5 years relative cure rate	75 %	35.7 %	40 %	14 %	0	9.8 %	33 %
				1939—41.			
Patients treated	37	37	74	25	26	51	121
Patients alive free of symptoms	25	17	42	7	3	10	52
5 years relative cure rate	68.5 %	45.5 %	56.6 %	28 %	11.5 %	19.6 %	43 %

In table II b we have divided the entire material into two periods. The first being that time where the surgeons were responsible for the

radium treatment (1928—37) and the second period covering the time in which the entire treatment was given by the radiologists (1938—41).

In table II c the material has been divided into three periods in such a manner that each period did contain a fairly equal number of patients. The tables show that the condition of the patient on admission for treatment are a little better the last 3 years, as more patients belong to stage 1 and 2. When comparing our stage distribution with the international statistics it appears that our material represents more stage 1 and 2. In each year stage 1 and 2 together have represented a little more than half of the patients. The reason for this, I suppose, can be a widespread public knowledge concerning the first symptoms of the disease, and the easy opportunity for the patients to consult a doctor both because of our sick insurance system and the small distances.

Method of Treatment

The *radium treatment* has roughly been unaltered throughout the whole period. We have given two radium treatments with an interval of about 8 to 10 days (with the exception of 1928 where three treatments were used). The total dose has been between 6 and 7,000 mgh. but in recent years in some cases with large cancer doses up to 8—9,000 mgh. have been applied. We have used a single tube in the uterine cavity and plate containers in the vagina. These containers vary in size from 4.2×3.4 cm. to 2.6×1.8 cm. We always make effort to introduce the largest possible container in the vagina and place it in such a manner that its longest diameter lies in the frontal plane in order to get as much radiation on the parametries as possible. In cancer with a cervical crater we use an egg shaped container.

Additional roentgen treatment is used for all patients, a smaller dose being used to patients belonging to stage 1 and 2 and a larger dose for stage 3 and 4. The routine treatment has been two abdominal and two sacral fields supplemented with a perineal field where the dose seldom surpasses 900 r. During the first years of this investigation the total dose was very small but later and for the longest period the total dose has been about 6,000 r. (in air). In the last three years even doses up to 10,000 r. have been used, which means an average dose upon each parametrium of between 2—2,500 r. roughly estimated.

How large the actual radium dose measured in r. is in the cervix and the parametries is difficult to estimate, but measurements I had the opportunity to make during a visit at Radiumhemmet in 1943—1944 concerning the distribution of the radiation under the standard condition used there for the radium treatment showed the following results: The average dose upon the surface of the cervix reaches 6—

2,000 r.; from here on the intensity of the radiation decreases quickly to all sides, but $2^1/_2$ cm from the middle of the cervix the radiation is still 6,000 r.; along the pelvic wall 5—6 cm. from the middle of the cervix the measurements show a radiation intensity of between 500 and 1,000 r. The measurements, which have not been published, have been made with SIEVERT's condensor chambers (I am much indebted and very thankful for the help, which S. BENNER and J. HEYMAN offered during the investigation). The experiment shows the importance of using supplementary roentgen treatment for a cancer spreading to the parametries in order to reach these.

In 1938 some changes were made in our treatment. At first we altered the sequence of the roentgen and radium treatment so that we finish the roentgen treatment before the radium treatment is started; thereby giving the cancer a chance to clean up and the patient to improve her condition before radium treatment is started. We have been much impressed as to how much the cancer has diminished and sometimes nearly disappeared after roentgen treatment alone and we feel that one ought to continue along these lines. Secondly we have tried to increase the distance from the vaginal applicator to the tumor in the cervix introducing a plate of wood or stents compound (these being of a thickness from $^1/_2$—1 cm.) between the cervix and the radium applicator; the thought being to counteract the quick decrease of the intensity of the radiation inside the deeper part of the tumor, and make the radiation in the tumor a little more homogeneous. One cannot predict how much this change alters the effect of the treatment.

The Results of Treatment

The results of our treatment are shown in table II. The absolute 5 years cure rate is 32.2 % during the whole period of investigation while the relative cure rate is 32.9 %. Table II a gives the result for the whole period grouped into the four stages. The relative cure rate for the earlier defined period lasting from 1928—1937 is 26.0 % and for the period 1938—1941 is 42.2 % as shown in table II b. This improvement cannot alone be explained by the small change in the patients condition to the better. The most pronounced improvement is seen in the 2 worst stages (3 and 4) where the cure rate is increased from 4.5 % to 20.3 %.

This also holds true if one divides the materials into 3 equal periods, as defined in table II c. The improvement of the results in the 3rd period is seen in all stages, but is most striking in the stages 3 and 4, where the corresponding figures for the three periods are 3 % —, 9.8 % — 19.6 %.

From these small figures no final conclusion can be made, but if we

should indicate some reason for the better result in the last period. It seems probable that the more large roentgen doses used at that time may have some importance.

Experience shows that the permanency of the cure of cancer of the cervix is relatively high and much better than that of the cancer of the breast because the cancer of the cervix has a smaller tendency to distant metastases than the former. We have not seen distant metastases in the bones, but in few cases the pelvic bones have directly been involved following the spreading of the cancer in the parametries. One is therefore allowed to expect, that the 10 years cure rate will not be very much below that of a 5 years period.

Of the 186 patients, treated 1928—36, 47 were alive and free of symptoms after the first 5 year period. 6 of these patients died in the second 5 year period, 4 of cancer and 2 of intercurrent diseases, and one was lost sight of. 40 patients were alive and free from symptoms after 10 years.

The 5 years relative cure rate in this material therefore is 25.3 % and the 10 years cure rate is 21.4 %.

Table III.

Evaluation of the results of treatment of cancer of the cervix arranged according to age-groups (10 years).

Age-groups	20—30	31—40	41—50	51—60	61—70	71—80	Total
Patients treated	26	87	105	86	55	12	365
Patients alive free of symptoms	6	33	40	29	10	2	120
5 years relative cure rate	23 %	36.7 %	38 %	37.7 %	18.3 %	16.7 %	32.9 %

The opinion has been expressed, that the cancer of the uterus has a very malignant course in young women. The question is not yet solved, because it is difficult to registrate a sufficient number of such cases. Our material is of course too small to make an important statement on the question, but perhaps it can be of some interest to publish our cure rates in the different age-groups for a comparison as done in table III a. It will be noticed that the cure rate is smaller for patients who are less than 30 years of age or more than 60 years old, this last mentioned group commonly representing poor cases in which relatively many have died from intercurrent diseases. The 113 patients belonging to the first and second age-group (20—40 years) in Table IV are divided into two groups: one group consisting of those in whom the disease started in connexion with pregnancy and the other, when this was not the case. It will be seen that when a cancer has started in connexion with pregnancy the cure rate is only 8.6 %, while the cure rate for the other group

more or less is of the same magnitude as the relative cure rate for the whole material.

Table IV.

Division of the patients belonging to the first and second age-group (20—40 years) in table 7 into two groups with regard to whether the cancer of the cervix has developed in connexion with pregnancy or not.

	Developed in connexion with pregnancy	Not developed in connexion with pregnancy	Total
Number of patients treated	23 (11 + 12)	90 (15 + 75)	113
Number of patients alive free of symptoms	2 (0 + 2)	37 (12 + 19)	39
5 years relative cure rate	8.6 %	41 %	34.5 %

The figures in the brackets show the distribution in the two age-groups.

The conclusion must be, I think, that patients in whom a cancer has started in connexion with pregnancy develop a more malignant form.

It is known that the interval between the appearance of the first symptom of the disease and the beginning of the treatment does not indicate anything about how much the disease has spread in this interval. This material has also been analyzed concerning this particular matter and the results are given in table V a. It appears that of the patients coming for treatment within a month after the first symptom was noticed not less than 31 % already belong to stage 3 and 4, while of the patients having symptoms for more than a year or even 2—3 years not less than 55.5 % belong to stage 1 and 2. Table VI shows the fate of the patients when these are grouped according to the duration of these symptoms prior to treatment. The relative cure rate does not differ much.

Table V.

Relation between the length of time elapsed from the appearance of the first symptom of the cancer of the cervix and the condition — termed in stages — at the time of our examination.

Duration of symptoms	Number of patients			Per-centage	Number of patients			Per-centage	Total	Per-centage
	Stage I	Stage II	Stage I + II		Stage III	Stage IV	Stage III + IV			
One month or less	20	14	34	69 %	10	5	15	31 %	49	43.4
One to three months	23	27	49	54.4 %	29	12	41	45.6 %	90	33.3
Three to six months	21	35	56	56 %	32	13	45	44 %	101	32.6
Six months to one year	17	17	24	30.4 %	25	17	42	63.6 %	66	27.4
One year or more	17	16	33	55.5 %	17	9	26	44.5 %	59	29.0
Total	87	109	196	54.8 %	113	56	169	45.2 %	365	32.9

Table VI.

Evaluation of the result of the treatment of cancer of the cervix arranged according to the duration of the symptoms prior to treatment.

Duration of symptoms	Patients treated	Alive, free of symptoms	5 years relative cure rate
One month or less	49	21	43 %
One to three months	90	30	33.3 %
Three to six months	101	33	32.6 %
Six months to one year	66	18	27.4 %
One year or more	59	18	29.0 %
Total	365	120	32.9 %

It is perhaps worth to notice that of the patients coming for treatment at least one year after the first symptom 29 % are cured.

Nearly all the cases must be classified as platecell carcinoma on histological classification and only 11 cases represent adenocarcinoma, of these three have been free of symptoms five years after treatment.

Table VII shows the fate of the patients, who were not cured five years after treatment. Of these 244 died within seven years after treatment, 73.5 % died before two years had elapsed. Of the patients, not cured, only 8 survived the five years limit.

Table VII.

A general view of all deaths among patients treated for cancer of the cervix within a 7 years period. The material is arranged according to the interval between the treatment and the death of the patient.

Died within	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Number of patients	107	179	215	228	236	241	244
Percentage	43.8	73.5	87.5	93.5	96.5	98.5	100

When estimating the value of the radiological treatment of the cancer of the cervix, also the palliative effect of the treatment must be considered. Of the 244 patients not cured in a five years period 94 (*i. e.* 38.5 %) have been releaved of these symptoms for a shorter or longer period (in stage I, 74 %; in stage II, 47.5 %; in stage III, 29 %, and in stage IV, 19 %).

Primary Mortality and Dangers of the Treatment

Even if it is the most common opinion, at least in Scandinavia, that the radiological treatment for cancer of the cervix is superior to the surgical treatment, we must admit that the radiological treatment also has

certain dangers and causes a primary mortality. The mortality rate is reported as very low. In our material we have had four patients who possibly died in connexion with the radium treatment, the cause of death being pelvic abscesses or pelvic peritonitis (one in stage II, two in stage III, one in stage IV). This constitutes a primary mortality of about 1.1 %.

It is sometimes unevitable to perforate the uterus, when it is difficult to find the cervical canal. This has occurred twice, but it did not in any of the cases cause any inconvenience, even no temperature rise.

The most important danger following the radium treatment is the late reactions from the rectum and the bladder, which can not completely be avoided, because the necessary tumor dose and the tissue tolerance dose are close to each other. As I have mentioned before, a proximate dose of 6,000 r. with the standard Stockholm dosage will be found ca. $2^1/_2$ cm. apart from the middle of the cervix. The distance between the applicator and the rectum and to the bladder will change a good deal depending upon the width of the vagina and the possibility of dilatating the vagina by the tamponade, and in some cases the distance may not be more than 3 cm. from the middle, sometimes perhaps less. The complimental roentgen treatment may sometimes increase the dose over the tolerance limit. The most publications indicate that rectum ulcerations are more often seen than those of the bladder and HEYMAN therefore states that the mucous membrane of the bladder is more resistant against the radiation than the mucous membrane of the rectum. That is not our experience. BRØBECK has reported a relatively high incidence of bladder lesions in an earlier publication from the Radiumcenter here.

Bladder reactions have been noticed in 20 cases, some of these have been mild and some severe with necrosis and incrustations appearing from one to six years after treatment. 18 of these occurred in the 5 years cured group and only two in the not cured group. Rectal lesions were seen in 17 cases and they appeared one to four years after the treatment. Ten of these patients belonged to the 5 years cured group, while the rest belonged to the group, who died from their cancer.

The above mentioned lesions were cured within $^1/_2$—2 years with the exception of 4, in which a fistula developed between the vagina and the rectum or the bladder or both. We must admit that the number of cases having the above mentioned lesions is surprisingly high, 11 % (41 of 365 cases). One of the explanations for this could be that we have been especially interested in these complications and followed the patients routinely with rectoscopy and cystoscopy, as well as questioned the patients thoroughly by each follow-up. As the lesions commonly develop relatively late neither the patient nor his doctor always recognize that symptoms from the bladder or the rectum can originate from the radio-

logical treatment, the patients being treated for a cystitis and proctitis, moreover the lesions vanish spontaneously and will not be mentioned, if not especially questioned at the follow-up. It is of special interest to report the percentage of reactions occurring in patients cured within an observation period of 5—18 years, as no figures have yet been published from any clinic on this matter. 120 patients have thus been cured within an observation period of 5—18 years and of these 32 cases have developed late bladder or rectal lesions (27 %), but between these only 4 cases (3.3 %) acquired lesions of an uncurable character, a somewhat consolating fact. The intensity of our radium treatment has not been extremely high about 6—7,000 mgh. nearly the same dose as used by HEYMAN (400 mgh. in the vagina and 2,500 mgh. in the uterus).

Cancer of the Body of the Uterus

The material

While all cases of the cancer of the cervix in Denmark are transferred to radiological treatment this is not the rule when a cancer of the body is diagnosed and our material is therefore to some extent selected, but it is difficult to say how much this is the case. The patients are transferred to our Radiumcenter from many different hospitals where the opinion differs a great deal as to the question: operation or radiological treatment. Because of the selection, our material certainly contains more patients in poor stages than would be the case in an unselected material. We have divided the material into three groups according to the definition made by HEYMAN, namely 1) clinically operable, 2) technically operable (*e. g.* cases who constitute a bad operative risk because of pronounced obesity, old age or associated diseases, such as a poor heart condition, diabetes, hypertension and this like), 3) inoperable cases.

In the period ranging 1928—1941 98 patients were examined with the view to treatment and 92 of these were radiologically treated, including those incompletely treated.

21 of the 98 patients (21.5 %) belonged to age-group 41—50 years, 32 (32.6 %) to group 51—60 years; 36 (36.7 %) to group 61—70 years and 9 (9.2 %) to group 71—80 years.

According to the distribution into HEYMAN's three groups, 36 patients belonged to the clinical operable group (39 %), 21 (22.8 %) the technical operable group, while 34 patients (38 %) were thought inoperable.

The histological diagnosis has in the most cases been that of adenocarcinoma, but in about 20 % no exact classification was made by the pathologist.

Method of Treatment

Until May 1940 the treatment used for cancer of the corpus of uterus was nearly the same as the above mentioned for cancer of the cervix applying one or sometimes two or three uterine tubes and a vaginal plate. Since 1940 the packing method worked out by HEYMAN has been adopted, the only change being made that we have not used a vaginal radium-applicator but in all cases have supplemented the radium treatment with that of roentgen. The roentgen dosage has been of the same magnitude as applied to the cancer of the cervix. We have used HEYMAN's equipment and have ordinarily used filter I or II these having either an outside diameter of 7.8 mm or 9.8 mm. The new even smaller filters have not been used in this material. The radium dose has been the same as proposed by HEYMAN, but each filter has enclosed a tube containing 10 mg. radium instead of 8 mg. Following each application we take a roentgen picture to be sure that the packing has been satisfactory. This method has been used for the treatment of in all 25 cases.

The Result of Treatment

Table VIII.

Results of treatment of cancer of the corpus with special reference to HEYMAN's *three groups.*

	Clinically operable	Technically operable	Inoperable	Total
Number of patients treated	36 (12)	21 (10)	35 (3)	92 (25)
Alive, free of symptoms 5 years	24 (10)	4 (1)	7 (1)	35 (12)
5 years relative cure rate %	66.5 (83.2)	19 (25)	20 (14)	38 (47.5)

The figures in brackets represent the number of patients treated by the packing method (HEYMAN).

Table VIII shows the result according to the three groups. In all 35 patients have been alive free of symptoms in a five years period, the absolute cure rate thus being 35.8 %, the relative cure rate 38 % and for the clinically operable group 66.5 %. Table VIII also shows the result of the packing method applied to 25 patients and the relative cure rate following this method of treatment is 47.5 % and for the clinically operable group 83 %. Our figures are not as nice as those quoted by HEYMAN, who has obtained a relative cure rate of 54 % with the old technique and 64 % with his packing method for all three groups together.

HEYMAN has investigated the five years cure rate following operative treatment for cancer of the body of the uterus and states that it is 55 % or less. In our material the corresponding figures for clinically operable

cases seem to be a little better. Therefore the material perhaps indicates that it is justifiable to use radiological treatment at least as an alternative treatment in operable cases of cancer of the corpus.

Table IX.

The results of treatment of the cancer of the corpus with special reference to the results in the different age groups.

Age-groups:	41—50	51—60	61—70	71—80	Total
Number of patients treated	20	28	35	9	92
Number of patients free of symptoms	14	12	9	0	35
Relative 5 year cure rate	70 %	42.5 %	25.7 %	0	38 %

The relative cure rate in four different age-groups are detailed on table IX. The good results are rapid diminishing with increasing age, and radium treatment to patients in the preclimacterial group has the best prognosis exactly in the same group which is most suitable for operation.

If we consider the time elapsing from the first symptom of the disease to admission to the clinic, we will notice that a large percentage of patients are coming very late for treatment, not less than 28.4 % have had symptoms in over 1 year up to 6 years. (In cancer of the cervix the corresponding figure was 16.2 %.) Cancer of the corpus is thus a very treacherous and sneaking disease. The course is relatively benign and the expansion slow; this is borne out by the fact that cure rate does not decrease even in cases which have reported late for treatment (table X).

Table X.

Evaluation of the result of treatment of cancer of the corpus arranged according to the duration of the symptom prior to treatment.

Duration of symptoms	Patients treated	Alive, free of symptoms	5 years relative cure rate
One month or less	14	6	43 %
One to three months	17	7	41.4 %
Three to six months	20	3	15 %
Six months to one year	15	7	46.5 %
One year or more	26	12	46 %
Total	92	35	38 %

57 patients died within a five year period, and of these 23 (40 %) died within less than 1 year; 41 (72 %) within less than 2 years; 48 (84.4 %) within less than 3 years; 50 (96.5 %) within less than 4 years since the beginning of the treatment.

At last it must be mentioned to the credit of therapy that 43.5 % of the patients not cured, were primarily relieved of their symptoms.

Mortality and Dangers following Treatment of the Cancer of the Corpus

3 patients have died in possible direct connexion with the radium treatment (3.2 %).

We have perforated the uterus four times, but have in all cases omitted the radium treatment in the same seance. We have seen no unpleasant consequences following these perforations.

We have experienced five late radium lesions of the bladder or the rectum starting from 1—4 years after the treatment; all these lesions have been cured. An additional case has been reported by OLESEN, in which a radium necrosis appeared 8 years after the radium treatment; this caused a fatal bleeding. By the post mortem our pathologist found no evidence of cancer.

Main Results

Cancer of the cervix: 373 patients were examined; 365 were treated. 120 were free of evidence of disease after 5 years with an absolute cure rate of 32.2 %, and a relative cure rate of 32.9 %, 29.8 % were in stage I with a relative cure rate of 69 %, 32.6 % in stage II with a relative cure rate of 38.6 %, 103 in stage III with a relative cure rate of 13.4 % and 56 in stage IV with a relative cure rate of 7.1 %.

The results are increasingly better throughout the period, this is especially the case in stage 3 and 4. The author thinks it is possibly due to the more intensive roentgen treatment in the last period.

The author has experienced relatively many cases of late radiation reactions from the bladder and the rectum (about 11 %), but only 1.1 % permanent consequence (fistulas).

Cancer of the corpus: 98 patients are admitted for treatment, but only 92 treated. 25 patients are treated with the packing method published by HEYMAN. The relative cure rate for all patients treated is 38 % and for the clinical operable cases 66.5 %. For the few patients treated with the packing method the cure rate was 48 % and for the clinically operable cases 83 %. Radium treatment of cancer of the corpus uteri seems to offer the patients just as good a chance as operation even in operable cases.

SUMMARY

The author presents the results of radiological treatment of cancer of the cervix and of cancer of the corpus of the uterus at the Radium Center in Odense from 1928—41.

Cancer of the cervix: 373 patients were examined; 365 were treated. 120 were free of evidence of disease after 5 years with an absolute cure rate of 32.2 % and a relative cure rate of 32.9 %.

Cancer of the corpus: 98 patients were admitted for treatment, but only 92 treated. 25 patients are treated with the packing method published by HEYMAN. The relative cure rate for all patients treated is 38 % and for the clinical operable cases 66.5 %.

ZUSAMMENFASSUNG

Der Verfasser gibt eine Übersicht über die Resultate der radiologischen Behandlung von Karzinom des Collum und Karzinom des Korpus uteri in der Radiumstation in Odense (Dänemark) 1928—1941.

Cervixkarzinom: 373 Patienten sind untersucht, aber nur 365 behandelt worden. Die absolute Heilungsziffer nach 5 Jahren war 32.2 % und die relative Heilungsziffer 32.9 %.

Korpuskarzinom: 98 Patienten sind untersucht, aber nur 92 behandelt worden. 25 von diesen Patienten sind mit der sogenannten Packungsmetode nach HEYMAN behandelt worden. Die relative Heilungsziffer für alle die behandelten Patienten ist 38 % und für die Gruppe der klinisch operablen 66.5 %.

RÉSUMÉ

L'auteur fait la revue des résultats obtenus par le centre de radiothérapie de Odense (Danemark) dans le traitement radiologique du cancer du col et du cancer du corps de l'utérus de la période 1928—1941.

Cancer du col de l'utérus: 373 cas sont examinés, mais seulement 365 sont traités. Le taux absolut de guérison après 5 ans est 32.2 %, et le taux relatif est 32.9 %.

Cancer du corps de l'utérus: 98 cas sont examinés, mais 92 seulement sont traités. 25 cas sont traités avec la méthode de remplissage selon HEYMAN. Le taux relatif de guérison pour tous les cas traités est 38 %, et le taux de guérison des cas cliniquement opérables 66.5 %.

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AUS DER GYNÄKOLOGISCHEN ABTEILUNG DES ZENTRALINSTITUTS FÜR STRAHLENTHERAPIE ZU HELSINKI, FINNLAND (DOZ. DR. V. KAHANPÄÄ)

ÜBER DIE BEHANDLUNGSERGEBNISSE DER KOLLUMKARZINOME IM STRAHLENBEHANDLUNGSINSTITUT ZU HELSINKI AUS DEN JAHREN 1937—42[1]

von

V. Kahanpää und *J. O. Kankkunen*

Die Strahlenbehandlung des Gebärmutterkrebses in Finnland gründet sich auf die von FORSSELL und HEYMAN entwickelte sog. »Stockholmer Methode». Die Initiative wurde von WICHMANN genommen, dessen Verdienst es ist, dass im Jahre 1926 in der Gynäkologischen Abteilung der Universitätskliniken die Radiumbehandlung in Gang gebracht wurde. Die ersten dort erhaltenen Resultate (aus den Jahren 1926—30) hat CHYDENIUS veröffentlicht, und die späteren, welche z. T. aus der neuen Universitäts-Frauenklinik stammten, sind von TURTOLA gesammelt worden (aus den Jahren 1931—40).

Als im Oktober 1936 das Zentralinstitut für Strahlentherapie eröffnet wurde, gab CHYDENIUS seine Tätigkeit in der Frauenklinik auf und wurde zum Gynäkologen des neuen Instituts ernannt. Die Radiumbehandlung konnte also auf dem Boden seiner umfangreichen Erfahrungen auf diesem Gebiete begonnen werden. CHYDENIUS hatte im »Radiumhemmet» zu Stockholm unter HEYMANS Leitung studiert und bewahrte den innigen Kontakt mit den schwedischen Kollegen bis zu seinem Tode in Stockholm 1941. Schon während seiner Tätigkeit in der Frauenklinik erzielte CHYDENIUS schöne Resultate bei der Behandlung des Gebärmutterkrebses, und auch von den in dieser Arbeit veröffentlichten Fällen sind die meisten von ihm behandelt worden.

Da unser Behandlungsverfahren im Prinzip von der Stockholmer Methode, welche dank HEYMANS zahlreicher Veröffentlichungen den an der gynäkologischen Radiologie Interessierten allgemein bekannt ist, nicht wesentlich abweicht, kann unser Material vom rein wissenschaftlichen Standpunkt kaum viel wesentlich Neues bieten. Eine kurze kritische Betrachtung unserer Fälle und der erzielten Resultate dürfte den-

[1] Bei der Redaktion am 4. VI. 1947 eingegangen.

noch angebracht sein, denn die in der Praxis gewonnenen Erfahrungen haben ja neben dem Fortschritt der reinen Wissenschaft ihren eigenen Wert. Auf sie gründen sich z. T. auch die eventuellen behandlungstechnischen Verbesserungen, wenigstens so lange, bis in der Zukunft die endgültige Lösung des Krebsproblems vielleicht völlig neue Möglichkeiten zur Behandlung oder Prophylaxe des Gebärmutterkrebses mit sich bringt.

Unser Material beginnt beim Jahreswechsel 1936—37, zu welcher Zeit die Gynäkologische Abteilung des Strahlenbehandlungsinstituts mit Hilfe der im physikalischen Laboratorium des Radiumhemmet kontrollierten, verhältnismässig grossen Radiummengen ihre Tätigkeit aufnehmen konnte. Dem Institut standen nämlich über 6 g Radium sowohl für Brachy- als auch für Teleradiumtherapie sowie ausserdem moderne Röntgenapparate zur Verfügung. Wegen der erforderlichen 5-jährigen Kontrollzeit schliesst das Material mit dem 15. 5. 42 ab.

Unser Krankengut umfasst 524 Kollumkarzinomfälle, die während der genannten Zeit ins Strahlenbehandlungsinstitut geschickt worden waren. Weggelassen wurden nur die früher schon anderwärts behandelten Fälle, d. h. lediglich diejenigen Patientinnen, welche postoperative Bestrahlung erhielten, sowie diejenigen, welche nach einer Operation oder nach anderwärts verabreichter Strahlenbehandlung Rezidive bekommen hatten.

Bei der Gruppierung der Kollumkarzinome in verschiedene Stadien nach der Ausbreitung des karzinomatösen Prozesses haben wir genau die von der Hygieneorganisation des Völkerbundes im Jahre 1937 festgelegten neuen Definitionen befolgt, sowie den Anweisungen gemäss die Grenzfälle zum günstigeren von den beiden in Frage kommenden Stadien gezählt.[1] Desgleichen sind bei der statistischen Behandlung des Materials die international üblichen Prinzipien berücksichtigt worden, wobei jede eventuelle Verbesserung der tatsächlichen Resultate kritisch vermieden wurde.

Die Altersverteilung unserer Patientinnen geht aus folgender Tabelle hervor:

Tabelle 1.

Die Altersverteilung unseres Materials.

Alter Jahre	20 —24	25 —29	30 —34	35 —39	40 — 44	45 —49	50 —54	55 —59	60 —64	65 —69	Über 70	Summe
Fälle	1	3	26	42	95	98	103	76	43	26	10	523[2]
Fälle, %.	0.2	0.6	5.0	8.0	18.2	18.7	19.7	14.5	8.2	5.0	1.9	100.0

[1] J. HEYMAN: League of Nations Health Organisation. Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix. Genova 1939.

[2] In einem nur poliklinisch untersuchten Falle war die Angabe des Alters im Journal vergessen worden.

Wie in allen anderen genügend umfangreichen Materialien (z. B. HEYMAN und KNAUS) zeigt auch unsere Alterstabelle unter den 40—55-Jährigen die grösste Frequenz der Kollumkarzinome. Die jüngste von unseren Patientinnen war 21 und die älteste 78 Jahre alt. Das durchschnittliche Alter der Patientinnen war 49.6 Jahre.

Hinsichtlich der Fälle von verschiedenen Stadien haben wir beobachtet, dass das durchschnittliche Alter der im Anfang der Krankheit konstatierten Fälle etwas niedriger ist als das der fortgeschrittenen: I St. = 45.6 Jahre, II St. = 48.7 J., III St. = 50.0 J. und IV St. = 50.9 J. Dieser Umstand beruht offenbar darauf, dass die bei den jüngeren Frauen vorgekommenen Kontaktblutungen oft früher zur Feststellung der Krankheit führen. Auch KNAUS hat die gleiche Beobachtung gemacht.

Vom Auftreten des ersten blutigen Ausflusses bis zum Eintreffen im Krankenhaus waren bei unseren Fällen durchschnittlich 6.2 Monate vergangen, welche Zeit bei den beginnenden Fällen natürlich kürzer war als bei den schon fortgeschrittenen (I St. = 3.6 Monate, II St. = 5.1 M., III St. = 6.6 M. und IV St. = 7.8 M.).

Von der ersten ärztlichen Konsultation bis zum Eintreffen im Krankenhaus war durchschnittlich 1.3 Monat verflossen. Auch in dieser Hinsicht stellten sich die beginnenden Fälle etwas günstiger als die anderen (I St. = 0.8 Monat, II St. = 1.1 M., III St. = 1.3 M. und IV St. = 1.4 M.). Das bei einigen Fällen stark verzögerte Eintreffen im Krankenhaus, welches die genannten Mittelwerte beeinflusst hat, beruht auf den in der Literatur häufig erwähnten *Versäumnissen der Ärzte* — besonders insofern, als die betreffende Patientin nicht gründlich untersucht worden ist. In einer anderen Veröffentlichung (KAHANPÄÄ) ist diese Frage näher besprochen worden.

Die Zeitspanne vom Auftreten der ersten Symptome bis zur ersten ärztlichen Konsultation lässt sich leicht aus den obigen Daten ermitteln: I St. = 2.8 Monate, II St. = 4.0 M., III St. = 5.3 M. und IV St. = 6.3 M. Durchschnittlich vom ganzen Material = 4.9 Monate. Die *Indolenz der Patientinnen* selbst hat also grossen Anteil daran gehabt, dass sich die Krankheit in vielen Fällen schon vor dem Eintreffen im Krankenhaus zu einem prognostisch ungünstigen Stadium entwickelt hatte. — Von ESCHS 298 Kollumkarzinomfällen hatten sich 48 % erst dann an den Arzt gwandt, als die Krankenheitssymptome schon länger als 3 Monate angedauert hatten.

Wie in CHYDENIUS' und auch in TURTOLAS aus der Frauenklinik stammendem Material sind auch *unsere Kollumkarzinome zum grössten Teil schon weit fortgeschrittene Fälle des III und IV Stadiums* gewesen. Solche enthält unser Material nämlich 341 oder 65 % von allen.

Im Vergleich zu CHYDENIUS' Material (1926—30), in welchem die weit fortgeschrittenen Fälle des III und IV Stadiums 89 % ausmachten, wäre die Beschaffenheit des in Finnland zur Behandlung gekommenen Kollumkarzinommaterials im Lauf der Jahre dennoch besser geworden. In gleicher Richtung weisen auch TURTOLAS Zahlen. In seinem umfangreichen Material, 953 Fälle aus der Frauenklinik in den Jahren 1931—40, machten das I und II Stadium ca. 40 % aus, und entsprechend die schlechten Fälle ca. 60 %. In den letzten Jahren des Materials wäre in der Beschaffenheit des Krankengutes eine Wendung in günstiger Richtung eingetreten, so dass seit 1937 über 60 % günstige Fälle waren. Diese augenscheinlich günstige Entwicklung dürfte jedoch mit gewisser Vorsicht aufzunehmen sein. Im Material der Frauenklinik sind nämlich nicht alle in der Poliklinik gewesenen Fälle enthalten, sondern nur die-

jenigen, welche in der Klinik behandelt worden waren. Während des Winterkrieges und der damit verbundenen unruhigen Zeiten dürften aus der Poliklinik manche Fälle weggeschickt worden sein, welche unter normalen Verhältnissen zur Behandlung aufgenommen worden wären. Dieser Umstand hat möglicherweise die Besserung des klinischen Materials der Frauenklinik in den letzten Jahren bewirkt, so dass es vielleicht kein richtiges Bild von den tatsächlichen Verhältnissen gibt.

Das Material des Strahlenbehandlungsinstituts, welches, wie gesagt, sämtliche Fälle umfasst, unabhängig davon, ob sie behandelt worden sind oder nicht, stützt auch nicht die Auffassung, dass das Krankengut in den betreffenden Jahren sich in günstiger Richtung verändert hätte. Die relative Anzahl der vorteilhaften Fälle des I und II Stadiums zeigte nämlich unregelmässige jährliche Schwankungen (40—26—25—31—52—32 %), welche offenbar nur zufälliger Natur gewesen sind.

Die schlechte Beschaffenheit unseres Materials hat dazu geführt, dass nicht alle Fälle zur Behandlung aufgenommen werden konnten, oder dass die Behandlung zwangsläufig unvollkommen, palliativ gewesen ist. *Gänzlich unbehandelt sind 58 Frauen oder 11.1 % von allen Fällen heimgeschickt worden* — völlig hoffnungslose Fälle, bei denen die Ausbreitung des karzinomatösen Prozesses, die multiplen Fernmetastasen oder der elende Allgemeinzustand nicht einmal einen Versuch zu palliativer Behandlung zuzulassen schienen.

Bei allen 466 in unserem Institut behandelten Fällen ist die Diagnose auch histologisch bestätigt worden. Ausserdem steht auch von einem Teil der als hoffnungslos abgewiesenen Fälle die Gewebsprobe zur Verfügung.

Bei 40 von den zur Behandlung aufgenommenen Patientinnen ist die Strahlentherapie ganz ungenügend gewesen, weil Ra-Behandlung nur einmal in palliativem Sinne verabreicht werden konnte, oder aber nur aus psychischen Gründen, »Solaminis causa», gegeben wurde. Von diesen Frauen hatte eine Karzinom des II, 11 des III und 28 des IV Stadiums. Dass die Behandlung auch einiger günstiger Fälle unterbrochen wurde, ist auf die Kriegsverhältnisse zurückzuführen. Wegen Bombenschäden musste das Krankenhaus während des Krieges zur Reparatur des Gebäudes einmal auch vollständig geräumt werden. — Obwohl die Behandlung der oben erwähnten 40 Patientinnen so mangelhaft gewesen ist (durchschnittliche Radiumdosen: Uterus 725 und Vagina 1,810 mg/St.), dass keine Hoffnung auf Heilung bestand, so haben wir auch diese Fälle bei der Berechnung der »relativen Heilung» mitgenommen.

Den übrigen 426 Patientinnen ist Brachyradiumtherapie 2—5 mal verabreicht worden, meistens jedoch (359 Fälle) 3 mal, was als die normale Methode des Instituts anzusehen ist. Es wurde gleichzeitig sowohl intrauterine als auch vaginale Behandlung angestrebt, und die Applikation ist auch bis auf einige wenige Ausnahmen immer gelungen. Bei jeder

Applikation betrug die Behandlungszeit ca. 22 Stunden. Wenn das Fieber über 39° stieg oder sich alarmierende Komplikationssymptome einstellten, wurden die Radiumpackungen schon früher entfernt.[1] Somit ist die Ra-Dosierung durchschnittlich folgende gewesen:

Bei einer Applikation: Ut. 1,100 + Vag. 1,570 = 2,670 mg/St.
Insgesamt: *Ut. 3,300 + Vag. 4,710 = 8,010 mg/St.*

Die Dosierung ist also etwas reichlicher gewesen als im Schema der Stockholmer Methode:

HEYMAN: Ut. 2,400 + Vag. 4,500 = 6,900 mg/St.

Auch bei uns sind jedoch bedeutende individuelle Schwankungen in der Dosierung berücksichtigt worden. Z. B. bei grossen exophyten Tumoren sind die vaginalen Dosen im allgemeinen bedeutend reichlicher als durchschnittlich gewesen, insbesondere wenn die Weite der Vagina eine effektive Tamponierung zum Schutze des Enddarms zuliess. Wenn die Vagina enger war, sowie in denjenigen Fällen, bei denen sich ein Krater gebildet hatte, ist die vaginale Dosierung dagegen oft kleiner als durchschnittlich gewesen. Noch vorsichtiger wurde die Behandlung bei senil-atrophischen Genitalien eingerichtet. In manchen Fällen ist der Enddarm ausser durch Tamponierung auch durch eine Bleiplatte geschützt worden. — Reizerscheinungen von seiten des Rektums, wie andauernder Durchfall und zeitweilige Blutungen sind indessen nicht ganz selten gewesen, aber schwerere Komplikationen, vor allem rekto-vaginale Fisteln, sind nur in einzelnen, ganz wenigen Fällen vorgekommen.

CHYDENIUS erwähnt über seine Dosierung nur kurz, dass »Radiumhemmets dos (4,500 mgrt.) blott sällan överskridits». — Bezüglich des späteren Materials der Frauenklinik werden folgende Behandlungsdosen angegeben:

TURTOLA: Ut. 2,448 + Vag. 3,774 = 6,222 mg/St.

Röntgenbestrahlung ist im allgemeinen sofort nach Abschluss der Radiumbehandlung verabreicht worden, in einigen Fällen indessen auch vorher, wenn die Patientin wegen Platzmangel nicht sofort zur Radiumbehandlung ins Krankenhaus aufgenommen werden konnte. Die Bestrahlung wurde aus je zwei Bauch- und Rückenfeldern auf beiden Seiten gegen die Parametrien gerichtet, um die Wirkung der Ra-Therapie in

[1] Seit Anfang 1945 ist die Behandlung nur aus den letzteren Gründen unterbrochen worden, nicht mehr auf Grund blossen Fieberanstiegs. Obwohl uns die Gefahren der inflammatorischen Komplikationen im Zusammenhang mit der Ra-Therapie durchaus bekannt waren, sind wir mit dieser neuen Behandlungsrichtung zufrieden gewesen, und werden in anderem Zusammenhang näher darauf zurückkommen. — Mit prophylaktischer Sulfa-Behandlung hingegen haben wir keine Resultate erzielt (KAHANPÄÄ).

dieser Gegend zu verstärken. Die Bestrahlung ist durchschnittlich in einer Serie von 31 Tagen verabreicht worden, wobei die Sonn- und Feiertage die einzige Unterbrechung bildeten. Auch das vollständige Blutbild ist während der Behandlungszeit genau verfolgt worden.

Die berechnete Tiefendosis gesondert in beide Parametrien betrug durchschnittlich 2,440 r. und war somit etwas grösser als die in Stockholm übliche. Unsere Dosierung variierte jährlich nur unwesentlich. Auch bei den Fällen der verschiedenen Stadien wichen die Dosierungen nicht viel voneinander ab: I St. = 2,480 r., II St. = 2,460 r., III St. = 2,370 r. und IV St. = 1,860 r. Demnach scheinen nur die allerschlechtesten Fälle weniger Röntgenbestrahlung erhalten zu haben als die übrigen, was aber nur darauf zurückzuführen ist, dass die Behandlung bei einigen derartigen Fällen wegen des geschwächten Allgemeinzustands oder während der Behandlung aufgetretener Komplikationen unterbrochen werden musste.

Bei der näheren kritischen Betrachtung unseres Materials konnten wir — ebensowenig wie HEYMAN — *nicht feststellen, dass die Röntgenbehandlung in der obigen Dosierung irgendwelche mit Gewissheit nachzuweisende Bedeutung für die Behandlungsergebnisse gehabt hätte.* — Zur Röntgen-»Kontaktbestrahlung» durch die Vagina (a. m. SCHÄFER und WITTE) haben wir wegen Mangel an Apparaten noch keine Gelegenheit gehabt.

Von den im Strahlenbehandlungsinstitut behandelten 466 Patientinnen starben während des Aufenthalts im Krankenhaus 13, so dass *die Primärsterblichkeit also 2.8 ± 0.8 % ausmacht.* Die Todesursachen waren folgende: Sepsis 3, Peritonitis diffusa 2, Pelveoperitonitis 2, Paralysis cordis 1, Embolia 2, Pneumonia 2 und Uraemia 1. Von den Gestorbenen waren Fälle des II Stadiums 5, des III Stadiums 3 und IV Stadiums 5.

Bei CHYDENIUS war die Primärsterblichkeit 2.7 ± 1.1 %, in dem von TURTOLA dargelegten Material der Frauenklinik 4.6 ± 3.3 %, was, wie er feststellt, bedeutend mehr ist als die durchschnittlichen Zahlen in der Literatur (nach PANKOW ca. 2.3 %). Bei KNAUS ist die Primärsterblichkeit sehr niedrig, nämlich nur 1.1 %.

In diesem Zusammenhange möchten wir darauf hinweisen, dass bei der Berechnung der Primärsterblichkeit nach Strahlenbehandlung und insbesondere *beim Vergleich derselben mit der entsprechenden Operationssterblichkeit die Beschaffenheit der Materialien mehr als es üblich ist zu berücksichtigen wäre.* Die operierten Patientinnen sind regelmässig ziemlich jung, ihre anderen Organe gesund, und das Karzinom ist bei ihnen ganz im Anfangsstadium. Zur Strahlenbehandlung kommen — wo elektive Therapie geübt wird — dagegen die ältesten Patientinnen, diejenigen mit schlechtem Allgemeinzustand, solche mit Erkrankungen der anderen Organe sowie ferner alle diejenigen, bei denen das Karzinom schon weiter

um sich gegriffen hat. *Die Radiumbehandlung wird ausserdem in palliativem Sinne oft auch in ganz hoffnungslosen Fällen verabreicht.* Beim Vergleich zwischen den Primärmortalitäten der beiden Behandlungsverfahren könnte man also mit gutem Grund diese Umstände mehr beachten und beim Vergleich der Gefährlichkeit der Methoden nur die Fälle des I und II Stadiums berücksichtigen.

Nach Abschluss der klinischen Behandlung stellen sich die Patientinnen in gewissen Zeitabständen im Krankenhaus *zur Nachuntersuchung* ein, und in der Zwischenzeit machen sie brieflich Mitteilung über ihr Befinden. Wenn die Verbindung aus irgendwelchen Gründen unterbrochen wird, erkundigt das Krankenhaus sich mit Hilfe der Register- oder Kirchenbehörden nach der neuen Adresse oder nach dem Schicksal der betreffenden Patientin. Infolge der mit unseren Kriegen verbundenen Schwierigkeiten, in erster Linie wegen der Umsiedlungen von Ort zu Ort, *haben wir 31 Patientinnen aus den Augen verloren, ehe die Kontrollzeit von 5 Jahren abgelaufen war.* Von diesen waren I St. 1, II St. 13, III St. 14 und IV St. 3 Fälle.

Der gleiche Nachteil hat sich auch im Material der Frauenklinik bemerkbar gemacht. TURTOLA hat die verschwundenen Fälle vor Berechnung der Behandlungsergebnisse eliminiert, auf welchen Umstand er in seiner Veröffentlichung allerdings nachdrücklich hinweist. Wegen der Vergleichsmöglichkeiten mit den Resultaten der anderen Autoren haben wir es für sachlicher erachtet, diese Fälle mitzunehmen, wenn auch ein Teil der verschwundenen Fälle auf diese Weise offenbar die Behandlungsergebnisse etwas verschlechtert. Den gleichen Standpunkt vertrat auch CHYDENIUS.

Die absolute Heilung, worunter man wie bekannt die Anzahl der über 5 Jahre nach Beginn der Behandlung symptomfrei gebliebenen Patientinnen im Verhältnis zu allen konstatierten Fällen versteht, *ist in unserem Material 167/524, m. a. W. 31.9 ± 2.0 %.*

Bei CHYDENIUS war die entsprechende Zahl 21.1 ± 2.4 %. TURTOLAS Material aus der Frauenklinik umfasst nur die behandelten Fälle, so dass die absolute Heilung daraus nicht hervorgeht. Es seien hier noch die absoluten Heilungsziffern aus dem *Radiumhemmet* zu Stockholm angeführt: In den Jahren 1914—30 = 21.9 %, später variierten sie jährlich zwischen 19.6—39.9 %, wobei sie in den letzten Jahren Tendenz zur Besserung gezeigt haben. Bei KNAUS war die absolute Heilung 35.3 %.

Die relative Heilung, worunter die Anzahl der länger als 5 Jahre symptomfrei Gebliebenen im Vergleich zu allen Behandelten verstanden wird, bietet eine andere Basis für die Beurteilung der Behandlungsergebnisse. Der Prozentsatz der Geheilten wird aus den verschiedenen Stadien gesondert sowie auch aus allen zusammen berechnet. Da die

Tabelle 2.

Die relative Heilung der Kollumkarzinome nach Strahlenbehandlung.

Karzinom Stadium	Anzahl d. behand. Fälle				Am Leben nach 5 Jahren				Am Leben, %			
	Chydenius	Turtola	Wir	Heyman	Chydenius	Turtola	Wir	Heyman	Chydenius	Turtola	Wir	Heyman
I	3	50	25	133	3	31	22	89	—	62	*88*	67
II	19	223	156	782	13	88	84	344	68	39	*54*	44
III	57	353	216	490	17	69	57	111	30	20	*26*	23
IV	122	195	69	206	9	7	4	17	7	4	*6*	8
I—IV	**201**	**821**	**466**	**1,611**	**42**	**195**	**167**	**561**	**20.9 ± 2.9**	**23.7 ± 1.5**	**35.8 ± 2.2**	**34.8 ± 1.2**

Vergleiche in jedem Stadium einzeln durchgeführt werden, kann die verschiedene Beschaffenheit der Materialien die Endresultate nicht beeinflussen, so dass sie also eine zuverlässigere Vergleichsbasis für die von verschiedenen Seiten vorgebrachten Ergebnisse darstellt.

In Tabelle 2 sind die relativen Heilungszahlen aus dem Strahlenbehandlungsinstitut zusammengestellt. Die gleiche Tabelle enthält auch die entsprechenden Zahlen aus den beiden früheren finnischen Publikationen sowie Heymans Resultate aus dem Radiumhemmet zu Stockholm von den Jahren 1932—38.

Die Zahlen der Tabelle sprechen für sich. Wir können feststellen, dass *die Stockholmer Methode in unserem Strahlenbehandlungsinstitut den Kollumkarzinomfällen verschiedener Stadien ebenso gute Heilung gebracht hat wie in ihrer Heimat.* Dass bei Chydenius einige Prozentzahlen noch vorteilhafter sind, dürfte vielleicht durch die Kleinheit des Materials zu erklären sein.

Das von Turtola dargelegte umfangreiche Material aus der Frauenklinik bleibt hingegen hinter den anderen viel zurück. Obwohl auch hier versucht worden ist, die gleiche Methode zu befolgen, sind die Ra-Dosen bei den vaginalen Applikationen recht gering geblieben. Beim Durchgehen des Materials hat Turtola auch festgestellt, dass bedeutende technische Schwierigkeiten bei der Behandlung vorgekommen sind. Dies dürfte wohl darauf zurückzuführen sein, dass die Frauenklinik eine grosse und vielseitige Unterrichtsklinik ist. Wegen des lebhaften Wechsels der Hilfsärzte hat jeder junge Arzt nur 2—3 Monate Zeit, um sich mit der Brachyradiumtherapie der Kollumkarzinome vertraut zu machen, so dass die Fälle zum grossen Teil von Anfängern auf dem Gebiet der Radiologie behandelt werden.

Wir haben noch alle in unserem Krankenhaus behandelten Fälle *nach der histologischen Struktur des Tumors* eingeteilt, um zu ermitteln,

ob dieser Umstand möglicherweise Einfluss auf die Behandlungsergebnisse gehabt hat.

In der Literatur sind über die Radiosensibilität besonders der Kollum-Adenokarzinome ganz widersprechende Ansichten vorgetragen worden. Nach Döderleins Auffassung sind dieselben für Strahlenbehandlung ungeeignet, und denselben Standpunkt haben später u. a. Regaud und Hautberg vertreten. Wintz hingegen hielt die Adenokarzinome für besonders dankbare Objekte der Strahlenbehandlung, während Ward und Farrar ihrerseits nicht feststellen konnten, dass die Prognose der Adenokarzinome schlechter gewesen wäre als die der anderen. Kermauner war der Meinung, dass die histologische Struktur des Tumors keine entscheidende Bedeutung habe, sondern dass die Ausbreitung des Tumors und das ganze klinische Bild ausschlaggebend seien.

Im Material der Frauenklinik fand Turtola 55 Kollum-Adenokarzinome, von welchen nach der Behandlung 22 noch länger als 5 Jahre lebten. Die relative Heilung war also 40.0 ± 6.0 % und besser als bei den Plattenepithelkarzinomen. Er vermutet auch, dass »das Adenokarzinom bei Strahlentherapie besser zu heilen scheint als die übrigen Formen». Der Verfasser bedauert, dass das histologische Präparat nicht von allen Fällen der Frauenklinik genommen worden ist, es fehlte in 17.5 %.

Die widersprechenden Ansichten über die Radiosensibilität der Adenokarzinome im Kollum sind offenbar auf die Seltenheit dieser Karzinomform zurückzuführen. So sind von den in unserer Anstalt behandelten 466 Kollumkarzinomen, von welchen allen das histologische Präparat und das Gutachten des Pathologen zur Verfügung gestanden hatten, 22 Fälle Adenokarzinome, d. h. nur 4.3 % von allen. — Bei Ward und Farrar war das entsprechende Verhältnis 20/259 oder 7.7 %.

Tabelle 8.

Die relative Heilung im Verhältnis zur histologischen Diagnose und zum Stadium.

Histologische Diagnose	I		II		III		IV		I—IV	
	Lebt	Gest.	Lebt	Gest.	Lebt	Gest.	Lebt	Gest.	Lebt	Gest.
Ca. planocellulare	16	3	68	57	53	129	4	54	141	243
Ca. solidum	5	—	11	10	4	20	—	8	20	38
Ca. adenomatosum	*1*	—	*5*	*5*	—	*7*	—	*2*	*6*	*14*
Ca. spec. incert.[1]	—	—	—	—	—	3	—	1	—	4
Zusammen	22	3	84	72	57	159	4	65	167	299

[1] Vom Pathologen als deutliches Karzinom diagnostiziert, aber ohne genauere Angabe der Gruppe. Präparat nicht zu finden.

Nach der histologischen Struktur und dem Stadium des Tumors gruppiert sehen wir unser Material in Tabelle 3, aus welcher die relative Heilung im Licht dieser Faktoren hervorgeht.

Die Prognose der grössten Gruppe, der Plattenepithelkarzinome, scheint also weder in den verschiedenen Stadien noch in allen zusammen (vom St. I am Leben 84 %, St. II 54 %, St. III 29 % und St. IV 7 %, sowie I—IV 36.5 %) wesentlich von der relativen Heilung des gesamten Materials abzuweichen (vgl. Tab. 2). Bezüglich der Gruppen Ca. solidum und desgleichen Ca. adenomatosum scheinen die Verhältnisse ungefähr die gleichen zu sein wie betreffend Ca. planocellulare, soweit die geringe Anzahl der Fälle derartige Schlussfolgerungen zulässt. *Von den 20 Adenokarzinomen unseres Materials sind 6 geheilt, welches Verhältnis (30 %) kaum als schlechter als die relative Heilung des gesamten Materials (34.8 %) gelten kann. Auch in diesen Fällen scheint die Ausbreitung des karzinomatösen Prozesses für die Prognose von ausschlaggebender Bedeutung zu sein.*

Im Hinblick auf die volle Konkurrenzfähigkeit der Behandlungsergebnisse bei Strahlentherapie unserer beginnenden Fälle von Kollumkarzinom (I und II St.) auch mit den allerbesten bei operativer Behandlung erzielten Resultaten, sowie auf Grund des im allgemeinen viel geringeren Mortalitätsrisikos bei der Strahlenbehandlung können wir uns mit vollem Recht HEYMANS Standpunkt anschliessen, *dass auch die beginnenden Kollumkarzinome im Prinzip der radiologischen Behandlung zugeführt werden sollten*, eine Ansicht, die er gründlich motiviert schon auf dem Nordischen Gynäkologenkongress im Jahre 1927 vorgebracht hat, und die auch in Amerika viel Anhang gewonnen hat.

ZUSAMMENFASSUNG

Das Material umfasst 524 Kollumkarzinome (aus den Jahren 1937—42), von welchen nur 35 % günstige Fälle des I und II St. waren. Die 58 schlechtesten Fälle mussten sogar ohne palliative Behandlung weggeschickt werden. Die übrigen 466 Fälle sind gemäss den Prinzipien der Stockholmer Methode behandelt worden. Die Ra-Dosierung war im Durchschnitt: Ut. 3,300 und Vag. 4,710 = 8,010 mg/St. Die berechnete Rtg.-Tiefendosis betrug 2,440 r. auf beide Parametrien.

Die Primärmortalität war 2.8 ± 0.8 %, die absolute Heilung 31.9 ± 2.0 % und die relative Heilung: I St. 88 %, II St. 54 %, III St. 26 % und IV St. 6 %, I—IV St. $35.8 \pm \pm 2.2$ %. Bei allen behandelten Fällen war die Diagnose histologisch bestätigt worden. Die Prognose ist abhängig vom Ca-Stadium und von dem klinischen Bilde überhaupt, die histologische Struktur des Tumors scheint keine nennenswerte Bedeutung für die Prognose zu haben. Die erzielten Resultate sprechen dafür, dass auch die Kollumkarzinome des I und II Stadiums im Prinzip radiologisch behandelt werden sollten.

SUMMARY

The material comprises 524 cases of collum carcinoma (from 1937 to 1942) of which only 35 % were favourable cases of Stage I & II. The 58 worst cases had to be sent away without palliative treatment. The remaining 466 cases have been treated in accordance with the principles of the Stockholm method. The Ra dose was on the average Ut. 3,300 and Vag. 4,710 = 8,010 mg/hr. The calculated deep roentgen dose was 2,440 r on both parameters.

Primary mortality was 2.8 ± 0.8 %, absolute recovery 31.9 ± 2.0 %, and relative recovery I st. 88 %, II st. 54 %, III st. 26 % and IV st. 6 %, I—IV st. 35.8 ± 2.2 %. In all cases treated the diagnosis was histologically confirmed. The prognosis depends on the Ca-stage and, on the whole, by the clinical picture. The histological structure of the tumour seems to have no special influence on the prognosis. The results obtained are speaking in favour of a principally radiological treatment also of the collum carcinomas of st. I and II.

RÉSUMÉ

Le matériel comprend 524 cancers du col (des années 1937 à 1942) dont seulement 35 % étaient des cas favorables des stades I et II. Les 58 plus mauvais cas durent même être renvoyés sans aucun traitement palliatif. Les 466 restants ont été traités selon les principes de la méthode de Stockholm. La dose de radium a été en moyenne de 3,300 pour l'utérus et de 4,710 pour le vagin = 8,010 mg/hres. La dose profonde des rayons Roentgen d'après les calculs s'est élevée à 2,440 r. sur les deux paramètres.

La mortalité primaire a été de 2.8 ± 0.8 %, la proportion des guérisons absolues de 31.9 ± 2.0 %, et celle des guérisons relatives de 88 % au stade I, de 54 % au stade II, de 26 % au stade III, de 6 % au stade IV et de 35.8 ± 2.2 % aux stades I—IV. Dans tous les cas traités le diagnostic avait été confirmé histologiquement. Le pronostic dépend du stade du cancer, et d'une façon générale du tableau clinique; la structure histologique de la tumeur ne semble pas avoir d'importance pronostique appréciable. Les résultats obtenus militent en faveur de l'idée qu'en principe les cancers du col aux stades I et II devraient eux aussi être traités par les rayons.

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A CLINICAL REVIEW OF 262 CASES OF CANCER OF UTERUS[1]

by

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In England and Wales, excluding Scotland and Ireland, there were in 1945 out of a population of 38,157,000 civilians 74,291 deaths from cancer. Of these 4,372 died of Cancer of uterus, and 7,294 died of Cancer of breast. It is interesting to note that although the incidence of uterine cancer has decreased slightly that of cancer of the breast has steadily risen during the last years as is seen in the following table:

	1938	1941	1945
Cancer of Uterus	4,375	4,528	4,372
Cancer of Breast	6,778	6,958	7,294

It must be borne in mind, however, that during the war owing to the necessity of reserving thousands of beds in our hospitals for war casualties and owing to the shortage of surgical specialists, a large proportion of whom were serving abroad, many cancer patients were possibly inadequately treated. They had to wait months sometimes for a vacant bed in hospital or nursing home, and the use of Radium and roentgen therapy was often made impossible owing to bombardment from the air. This was especially the case in the early years of the war, when Radium had to be buried underground and many of the roentgen installations dismantled. For instance the Marie Curie Hospital with which I am connected, was completely destroyed by a bomb, and for some months we had to make use of beds allocated to us by another

[1] Submitted for publication, June 9, 1947.

hospital. Then too, owing to the sudden evacuation to the country of thousands of people from London, private practice suffered considerably, my own included, and it was a year or two before we were able to get into touch with some of our patients for the regular follow-up which is so necessary for research.

In my own gynaecological practice I owe much to my association with the Marie Curie Hospital, which draws its patients mainly from the surgeons of the South London Hospital, The Elizabeth Garrett Anderson Hospital, and the New Sussex Hospital, all hospitals staffed by Women Doctors only and from the Royal Free Hospital. Under the first Director Dr ELIZABETH HURDON and its present Director Dr GILMOUR a line of treatment was agreed upon and a large number of cases were treated by the same technique. In this work the interest and advice of Professor HEYMAN has been invaluable and the technique of the Marie Curie Hospital has been based on a modification of the Stockholm methods.

In my own series of cases *Cancer of Uterus* was not a very common disease. Of the 262 cases I have had 174 were Cancer of the Cervix uteri and 88 of the Corpus uteri, as compared with 993 cases of *Fibromyomata of Uterus and Metropathia haemorrhagica* and 291 *cases of Cancer of Breast.*

Of the 993 cases of Fibromyomata of Uterus amd Metropathia haemorrhagica I did a *hysterectomy* in 502, used *Radium* in 173 and *Deep roentgen therapy* in 318 cases. In 1914 I had installed a Roentgen Apparatus in my consulting rooms after seeing the good results obtained by KRÖNIG and GAUSS in Freiburg in the treatment of small fibromyomata and in 1922 I changed my apparatus for one of 200,000 volts, but unfortunately had to give it up during the war. Otherwise the number of cases treated by Deep roentgen therapy would have been greater and the number by Radium smaller as in many cases I have found the former method more certain and very satisfactory.

In the greater percentage of cases of *Cancer of Breast* I performed a major operation and followed it up with Deep roentgen therapy with good results. Radium needles were mostly used for local recurrences.

In deciding upon the best methods of treatment one can but be influenced by the end results, in spite of the fact that there must always be some danger in relying too much on statistics especially when dealing with a small number of cases. This is of course partly due to the different ages of the patients *e. g.* in my cases of Cancer of the Corpus 7 patients were over 70 years of age, and one could scarcely expect them to survive as long or longer than the age of 80.

Cases of Cancer of Cervix Uteri

I have had 174 cases in my practice up to the end of 1946. Of these the treatment employed was:

Panhysterectomy	23[1]	cases (in 15 followed by roentgen)
Deep roentgen therapy ..	6	
Radium.....	138	
Not treated	7	
	174	

Of these 169 were married and 5 were single.

The oldest patient was 77 and the youngest 27 years old.

In two patients there were coexistent fibroids.

In 1925 the work of the Marie Curie Hospital began under the Directorship of Dr HURDON and from that date I was able to treat 136 of my patients with Radium according to the Marie Curie Hospital technique. The classification of these was

Stage 1	5	cases
Stage 2	43	»
Stage 3	66	»
Stage 4	22	»
	136	cases

In two cases there was carcinoma of the cervical stump following Subtotal Hysterectomy for fibroids.

Technique

In a typical case the patient was admitted into Hospital or nursing home 2 nights before treatment, and Acriflavine vaginal douches were given. The temperature was watched and if raised the treatment was postponed.

Under an anaesthetic (Pentothal or evipan supplemented by gas and oxygen and ether if necessary) an intrauterine tandem was introduced containing two tubes each 3 cm long and containing 25 mg of Radium in each. Filtration 1.0 mm Pt in a rubber tube 1.5 mm thick. Three vaginal plaques were then placed in the vagina one in each lateral fornix as far out and as high up as possible against the pelvic wall, and the third was then placed over the cervix. Each plaque contained 4 5-mg needles with filtration 0.3 mm of Pt. The plaque was 25 × 20 × 6 mm

[1] In 10 of these, other surgeons had performed the operation, and had sent the patients to me for roentgen therapy.

made of silver 2 mm thick and was encased in a rubber screen 1.5 mm thick. The vagina was then tightly packed with gauze wrung out of acriflavine. The total dosage was given in 66 hours divided into 3 treatments of 22 hours each and given at intervals of one and two weeks. If the uterine cavity measured more than 7 cm long an extra tube was added. The average total dosage was 7,261 mghs.

Results at the end of 5 years in Primary cases of Cancer of Cervix treated by Irradiation to end of 1941

Classification	Number examined	Number treated to end of 1941	Living at end of 5 years	Died of intercurrent disease	Survival rate at end of 5 years
Stage 1	4	4	4		100 %
Stage 2	41	40	22	1	55 »
Stage 3	62	61	18	2	29.5 »
Stage 4	20	16	0		0 »
	127	121	44	3	36.3 %

Results at the end of 10 years in Primary cases of Cancer of Cervix treated by Irradiation to end of 1936

Classification	Number examined	Number treated to end of 1936	Living at end of 10 years	Died of intercurrent disease	Survival rate at end of 10 years
Stage 1					
Stage 2	20	20	11	2	55 %
Stage 3	46	45	11	4	24.4 »
Stage 4	18	14			
	84	79	22	6	27.7 %

Three Cases could not be traced but were assumed to have died of Cancer.

There were in all 4 cases of rectovaginal fistula. In all of these I did a colostomy. In one case there was a vesicovaginal fistula, but the patient was too ill to undergo operation.

Another case was of special interest as the recurrence in the rectum was late in developing and has responded to treatment. She now shows no sign of growth 2 years after treatment of the rectal ulcer.

Case of Cancer of Cervix and Secondary of Rectum ten Years after

Mrs H. aet. 51. one child.

1933. *Symptoms.* Metrorrhagia for last 6 months. She was worried because her mother had died of Cancer of Uterus. *Examination.* Fibrotic uterus the size of a 3 months pregnancy. Fungating growth of cervix. Stage 2. *Operation.* D & C and biopsy of cervix. *Path. Report.* Adenocarcinoma. Curettings scanty and non-malignant. *Radium Treatment.* Total Dosage 7,612 mghs in 3 treatments.

1935. Patient did well until 1935 when the vaginal haemorrhage returned. The cervix was healthy. Curettings showed degeneration and were copious. Two cylinders each containing 8 mg of Radium were introduced into the cornua and 66 mg in tandem into the uterus. This dose was repeated in one week and then in a fortnight. Total dosage 5,412 mghs.

1943. She did well until 1943 when she complained of haemorrhoids. Examination showed a ring of hard nodular small growths all round the lumen of the rectum 3 cm from the anus. They were smooth and there was no bleeding.

1945. In September these small fibrotic nodules were bigger and harder and defaecation was more difficult. There was a small ulcer on the posterior lateral surface of the rectum. Mr. GABRIEL, the rectal specialist, saw the case with me and we did a biopsy. Path. Report by Dr DUKES of St. Barts Hospital confirmed a somewhat atypical adenocarcinoma not resembling the common types of rectal carcinoma but closely resembling the original cervical growth and consequently he was of the opinion that it was a recurrence. I therefore introduced a plaque containing 20 mg of Radium into the vagina on the lateral wall against the Rectal ulcer (dosage 360 mghs) followed 3 months after with 50 mg in rectal tube (dosage 1,000 mgh). She did well and in 1947 there is no growth, and except for some constriction of the anal canal due to fibrosis which has to be dilated from time to time, she is very well and suffers no discomfort.

Cases of Cancer of the Corpus Uteri

I have had 88 cases in my practice up to the end of 1946, a large proportion compared to the 174 cases of Cancer of Cervix. The treatment employed was:

Hysterectomy	51	cases
Radiotherapy.....	33	»
Laparotomy	4	»
	88	cases

Of these 58 were married and 30 single. The oldest patient was 78 and the youngest 33 years old. Two cases are included under Radiotherapy although they had Hysterectomy following full dosage of Radiotherapy, one 20 years after and one 3 months after Radium treatment and one week after a 1,500 r dose of roentden therapy. The former did well and the latter died 2 months after.

Hysterectomy

Of the 51 cases of Hysterectomy I did a *subtotal Hysterectomy* in 2 and a *Panhysterectomy* in 39 cases. Of the 12 *subtotal Hysterectomies* 2 were not traced after the first year, 2 were alive and well, one 10 years and one 16 years after operation, 5 were alive and well 5 years after 2 lived under 5 years and one died 24 hours after operation, of cardiac failure. In two of these cases it was fortunate that I had decided on surgery rather than radiotherapy. For in one a married woman aet. 54 I was obliged to do a resection of 6 inches of pelvic colon with end to end anastomosis as there was extension of growth into the colon, but no invasion of the mucous membrane. Path. Report: Adenocarcinoma. The patient was alive and well 13 years after operation.

In the second case a single woman aet. 53, a bad subject for operation, a loop of small intestine was firmly adherent to the fundus uteri. It was resected and a side to side anastomosis performed after closing the ends. The Path. Report showed necrotic adenocarcinoma extending into the mucosa of small intestine with a secondary growth in one ovary. The patient was alive and well at the end of 8 years.

Radiotherapy

33 cases were treated with Radium. In 4 of these pyometra with pyrexia was present or developed after one or two treatments and it was necessary to give several intra-uterine douches for a few days before introducing the Radium.

The Technique in a typical case was as follows. An intrauterine tandem consisting of 2 tubes each 3 cm long and containing 25 mg of Radium extends from the fundus to the external os. (If the uterine cavity is longer than 7 cm an extra tube is added.)

In addition and before placing the intrauterine tubes in position 2 small tubes or cylinders 1.1 cm in length and each containing 8 mg of Radium and mounted on long wires, are placed in the uterus extending transversely from the top of the central tandem to the cornua. Two vaginal plaques each containing 20 mg of Radium are placed in position one in each lateral fornix, avoiding the cervix if possible, and the vagina is then tightly packed with acriflavine gauze. The filtration is the same as that described in the Technique for Cases of Cancer of Cervix. The Radium is left in situ for 66 hours divided into treatments as described before, a total of 6,996 mghs being the average dose given.

Results in 88 Cases of Cancer of Corpus Uteri

Treatment	Number of cases	Living at end of 5 years. Treated before 1941	Survival rate	Living at end of 10 years. Treated before 1936	Survival rate
Hysterectomy	51	26	50.9 %	14[1]	27.4 %
Panhysterectomy .. 39					
Subtotal Hysterectomy 12					
Laparotomy	4				
Radiotherapy.....	33	18	54.5 »	10[2]	30,3 »
Total	88	44	50 %	24	27.2 %

Two cases were of special interest.

1. Case of Sarcoma of Fundus associated with v. Recklingshausen's Disease

Miss A. aet. 25.

1936. *Symptoms.* Severe menorrhagia for 4 years, with severe floodings on 4 occasions when she lost several pints of blood. In 1933 she had had a D & C and in 1935 a menorrhagia dose of Radium by another surgeon with no satisfactory result. She was then put on a long course of treatment including Progestin, Pregnyl, Progynon, Sistomensin etc.

Past History. When aged 12 she first suffered from multiple neurofibromatosis which was diagnosed first by Dr PARKES WEBER.

In 1936 she was sent to me for Deep roentgen therapy, and I gave her a full castration dose. She was anaemic and the uterus was the size of a $2^1/_2$ months pregnancy, freely moveable and the ovaries were normal. Although the menorrhagia considerably lessened, she developed an appendicitis so I removed the appendix in 1937 and at the same time examined the ovaries which I found normal. I also did a diagnostic D & C and the pathological report showed non malignancy.

1941. She was sent back to me as the menstrual periods although not so severe were becoming prolonged. In the meantime the neurofibromata were increasing in number all over the body including the scalp. I removed one for examination, the path. report confirming the diagnosis.

1942. In November a small uterine Polyp has extruded from the os. This I twisted off cauterizing the base. The *Path. Report:* fibroid polyp stangulated by the cervix, and is quite innocent. By December it had recurred. I therefore did a diagnostic D & C and removed the polyp. Clinically I believed it to be malignant but the Path. Report from the Marie Curie Hospital still showed it to be innocent.

[1] Of the *Hysterectomy* cases treated before 1936, 3 cases are alive and well 12 years after, 3 cases survived and are well 13, 14 and 16 years after, 2 are alive and well 19 years and one 23 years after treatment.

[2] Of the *Radiotherapy* cases 2 are alive and well 12 years after, 2, 13 and 16 years after 2, 17 and 18, and 2, 20 years after treatment.

1943. It recurred again and was bigger than before and friable. I therefore sent her back to the Professor (who had originally sent her to me) for Hysterectomy. This was done the report being »There was no evidence of abnormality so far as the abdominal organs were concerned. There were one or two small neuromata to be felt in the region of the obturator fossa and a larger softer nodule just internal to the anterior superior spine on the right side. The ovaries were very small but at the special request of the patient one ovary was left in situ.

Macroscopically. The uterus was found to contain a mass about the size of a plum, gelatinous cystic in places and with yellow areas. It appeared to arise from a firmer nodule in the wall of the uterus, the size of a small cherry.

Microscopically. Dr ROBB SMITH the pathologist diagnosed an endometrial sarcoma. He was unable to say positively whether it arose from a neuroma but sections from the cervix (which appeared to be normal on naked eye examination) showed the presence of small neuromata of nerve fibres. In the polyp there are also areas where the sarcoma cells are lying in a somewhat myxomatous stroma. The muscle of the body of the uterus appears natural and the endometrium seems to have shrunk to a single layer of epithelium immediately adjacent to the muscle.

Professor MATTHEW STEWART kindly looked at the slides for me and reports: »If, as I rather suspect, this is a neurogenic myxofibrosarcoma, then probably the malignancy is not of a very high grade, but I feel bound to label it sarcomatous.»

This prognosis appears to be correct as the patient is alive and well, in 1947.

2. Case of Cancer of Corpus associated with acute Pain and Fibroid of Uterus

Mrs D. aet. 56.

The patient was a red haired woman with 2 children. When I first saw her she had had a years illness and had been treated for advanced arthritis of the spine and knee.

She complained of Menorrhagia having had 2 very heavy periods and a slightly blood-stained discharge in the interval.

On examination I found a fibrotic uterus the size of a 3 months pregnancy. It was mobile and the parametria free. There was a small cervical polyp and erosion. I diagnosed a possible Carcinoma of Fundus and advised a diagnostic D & C.

Operation. This was done on March 7. 1942. The length of the uterus was 10 cm and there were a very few curettings. I put in 50 mg of Radium and a plaque of 20 mg to the cervix for 24 hours pending, the Path. Report. Dose: 1,680 mgh.

Path. Report. Curettings and cervical biopsy showed normal tissues.

The cervical polyp showed *Squamous Carcinoma.*

I therefore completed the Radium Treatment on March 14 and 28th a total dose of 7,400 mgh assuming that it was a case of very early Carcinoma of cervix. She did well and I did not then realise that the squamous carcinoma of the polyp was due to metaplasia and that the case therefore according to MEIGS presented a poor prognosis especially as in addition there was a *fibroid* present.

Two months afterwards she was sent back to me as she complained of *acute pain* worse at night. The pain was in both iliac fossae and extended down to the knees *Examination* showed that the uterus was smaller and the parametria free. There was very slight bleeding on examination.

Roentgen examination of pelvis and spine showed no secondaries but advanced osteo-arthritis of the lumbar vertebrae.

The attacks of pain increased in severity and were only relieved by Veganin or Morphia. Pain is noted by several observers to be of bad prognostic significance but the nature of the attacks which were sudden, made me think they might be due to some obscure abdominal condition. The urine was normal and there was no pyrexia or leucocytosis. I advised operation.

This she and her husband were adverse to, but she finally agreed to come in to the Marie Curie Hospital for Deep roentgen therapy for the pain and possible extension of the growth.

While in Hospital the pain became so severe that she consented to Operation.

I therefore did a *Panhysterectomy* and Appendicectomy. The cervical wall was enlarged by a soft fibroid 5 × 4 × 3 cm in size. The operation was easy and the patient stood it well.

Path. Report. There was extensive infiltration by solid adenocarcinoma of the uterine wall and this in spite of the fact that the uterus had had a 7,400 mgh dose 3 months before).

The lining of the uterus was macroscopically smooth and the fibroid showed some hyaline change but no malignancy.

Two days after, she started the whole tain of symptoms described by NORMAN MILLER[1] of Ann Arbor, Michigan, as due to radiation, and as he says forming a potent argument against preoperative radiation by those advocating surgery alone. Viz. Urethrocystitis, Haematuria, Hydronephrosis, Perinephritic abscess, Incontinence, Wound infection, Pelvic peritonitis and faecal fistula.

The haematuria was excessive starting on the second day after operation. (The only patient I have seen like it was a patient I treated with Radium 1,200 mchs for menorrhagia, which however recurred and I therefore gave her Deep roentgen therapy. She started with haematuria so severe that she was brought into Hospital almost moribund. She was delirious and so anemic that I did an immediate Blood Transfusion. A later cystoscopy and ureteral catheterisation showed no other cause and she recovered completely and had no further trouble.)

In this case, however, there was severe urethrocystitis as well and 6 days after, she developed a huge hydronephrosis and perinephric abscess. I operated and found about an ounce of creamy pus. 4 days later she developed a renal fistula. I questioned then whether it was a case of carbuncle of kidney or an ascending infection from the pelvis, but at that time I could find no trace of a pelvic abscess.

A month after the operation a sinus developed in the abdominal wound and a definite pelvic abscess was diagnosed. Then a faecal fistula developed and the patient went rapidly downhill and died 2 months after the Hysterectomy.

The main points of interest in this case seem to be

a) The difficulty in diagnosing Carcinoma of Corpus not involving the endometrium especially when it is a case of metaplasia.

b) That in spite of 7,400 mghs of Radium treatment the whole of the uterine wall was found to be invaded by adenocarcinoma, and only the cervical polyp showed squamous carcinoma.

c) That had I decided originally on preoperative radiation it would possibly have been better not to give more than one dose of 3,500 mghs of Radium and that having given even 1,150 r roentgen it would have been wiser to have postponed the operation for at least a month.

[1] Amer. Journal of Obst. & Gyn. Nov. 1940.

d) That the acute pain and the presence of the fibroid should have warned me that I was dealing with a case presenting a very serious prognosis.

Multiple Neoplasms associated with Cancer of the Uterus

In the 88 cases of Cancer of the Corpus Uteri, *Fibromyomata* occurred in 12. In one case a large degenerating fibroid was invaded by cancerous growth.

In 6 cases, Cancer of the Uterus was either preceded or followed by a primary Cancer of some other organ.

In 2 cases cancer of the corpus the patients died of *Cancer of stomach*, one 12 years after and the other 5 years after.

In 2 cases, Cancer of the fundus was preceded by *Cancer of breast*, one 2 years before and the other 8 years before.

One patient had a *retroperitoneal sarcoma* which was cured by operation followed by Deep roentgen therapy and died of Cancer of Fundus 18 years after.

Another patient had Carcinoma of Cervix and died 10 years after, of Cancer of Bronchus.

SUMMARY

From the author's clinical review one is justified in saying, that the incidence of Cancer of Uterus is not a high one, that in early cases the percentage of cures is high, and every effort should be made to induce patients to believe in its curability and to be examined as early as possible after the first symptoms appear; that Cancer of the Corpus is, in England, not so very uncommon as compared with Cancer of Cervix, and that its best method of cure is still uncertain, and lastly that in some individuals there appears to be a marked predisposition to Cancer, for the cure of the disease in one organ may, many years after be followed by a primary malignant growth in some other organ.

ZUSAMMENFASSUNG

Nach Verf.s klinischer Übersicht ist die Behauptung berechtigt, dass die Häufigkeit des Gebärmutterkrebses nicht gross ist, dass der Heilungsprozentsatz in frühem Stadium ein hoher ist, und dass man keine Mühe sparen darf, die Kranken von der Heilbarkeit des Leidens zu überzeugen und sie dazu anzuhalten, sich baldmöglichst nach Auftreten der ersten Symptome untersuchen zu lassen. Ferner dass der Korpuskrebs in England im Verhältnis zum Zervixkrebs nicht besonders selten vorkommt, dass die beste Behandlungsmethode desselben noch ungewiss ist, und schliesslich dass manche Menschen eine ausgesprochene Neigung zu Krebs zu haben scheinen, indem auf die Heilung der Krankheit in einem Organ viele Jahre später primäres malignes Wachstum in irgend einem anderen Organ folgen kann.

RÉSUMÉ

L'étude clinique à laquelle s'est livré l'auteur justifie l'assertion que la fréquence du cancer de l'utérus n'est pas grande, que dans les cas pris au début le pourcentage des guérisons est élevé, et qu'il faudrait faire tous les efforts pour convaincre les malades que le mal est curable et les amener à être examinées le plus tôt possible après l'apparition des premiers symptômes. Il ressort aussi de cette revue que le cancer du corps, en Angleterre n'est pas particulièrement rare, comparé au cancer du col, et qu'on a encore des doutes quant à la meilleure façon de le guérir; et enfin, qu'on constate chez certains individus une prédisposition marquée au cancer, attendu que la guérison du mal dans un organe peut être suivie, bien des années après, de l'apparition d'une tumeur maligne indépendante dans quelque autre.

HÔPITAL DE L'ÉTAT À SOENDERBORG, DENMARK. SERVICE DE GYNÉCOLOGIE ET D'OBSTÉTRIQUE (CHEF DE SERVICE: EKKERT PETERSEN)

TROIS CAS DE CANCER DU COL UTÉRIN PENDANT LA DERNIÈRE MOITIÉ DE LA GROSSESSE[1]

par

Ekkert Petersen

Le traitement du cancer du col utérin se fait en général sans égard à la grossesse et sans tenir compte du fétus. Le plus souvent la maladie est découverte au début de la grossesse où le sort du fétus ne peut être considéré qu'en arrière-plan.

Mais s'il s'agit d'une grossesse plus avancée l'idée de la possibilité de conserver le fétus ne peut pas être écartée, surtout quand il s'agit d'un petit cancer au début de son développement et sans le moindre signe d'une propagation en dehors du col uterin.

En trois cas j'ai eu l'occasion d'observer des cancers de cette catégorie où je l'ai jugé justifiable de tenter une guérison du cancer par traitement local au radium et ensuite attendre l'accouchement.

Dans la littérature à ma disposition je n'ai pas pu trouver des rapports sur un traitement pareil et il me semble que la publication de mes cas s'impose de ce fait.

Cas 1. Malade âgée de 35 ans; 2ième grossesse.

Admise à l'hôpital $^{18}/_{4}$—$^{9}/_{5}$ 1939.

Premier accouchement en 1938: normal.

Dernière menstruation au début de décembre 1938.

Au début d'avril 1939 petite hémorrhagie vaginale. Le médecin a trouvé une petite tumeur sur le col utérin, et une excision probatoire a montrée qu'il s'agissait d'une carcinome. Lors de l'admission on a trouvé le fond de l'utérus à la hauteur de la transversale ombilicale. Présentation de tête.

Sur la lèvre antérieure du col utérin on trouve une tumeur aplatie de la grandeur d'un pois.

Les entourages normaux.

Traitement: 2 fois à 10 jours d'intervalle émanation de radium (17 + 16 millicuries détruites) sur le col utérin. A la sortie de la malade la tumeur était complètement disparue. Suite de la grossesse normale. La malade était reçue à l'hôpital pour l'accou ne-

[1] Remis à la Réd. le 25 Mai 1947.

menv et le $^{4}/_{9}$ 1939 elle a mise au monde un enfant venu à terme. L'accouchement a duré 31 h res, la période de dilatation étant assez prolongée. Suites de couche normales. A la sorti e col utérin était tout normal, le corps utérin s'était bien réformé, et il n'y avait rien anormal aux côtés.

s années suivantes la malade s'est bien portée.

menstruation a été un peu plus faible qu'avant et un peu irrégulière. Pas de grossesse ultérieure.

ur un examen le $^{10}/_{5}$ 1947 on trouve le col un peu aplati, le corps utérin de forme, grand ur, position, consistance et mobilité normales et rien d'anormal aux côtés.

Cas 2. Malade âgée de 31 ans; première grossesse.

Admise à l'hôpital $^{20}/_{11}$ 1939—$^{3}/_{2}$ 1940.

Dernière menstruation fin mars 1939. Au début d'octobre petite hémorrhagie vaginale qui s'est répetée 3 fois.

Admise à l'observation de placenta praevia.

Le fond de l'uterus se trouve à une distance de 10 cm du proc. xiphoide. Présentation de tête.

Sur la lèvre postérieure du col utérin on trouve une tumeur irréguliere de la grandeur d'une noisette, saignante au toucher. Excision probatoire: carcinome.

Traitement: 2 fois à 10 jours d'intervalle émanation de radium (16 + 16 millicuries détr.) sur le col utérin. La tumeur a disparue.

Le $^{11}/_{1}$ 1940 accouchement d'un enfant vivant venu à terme. L'accouchement a duré longtemps (3 jours), et a dû être fini par l'application du forceps; à ce moment l'orifice utérin était complètement dilaté. A la sortie de la malade le col utérin était tout normal, le corps utérin de forme, grandeur, position, consistance et mobilité normales, et il n'y avait rien d'anormal aux côtés. La malade ayant quittée la contrée je n'ai pas eu l'occasion de l'examiner maintenant, mais par téléphone elle a donné le renseignement que la menstruation a été régulière, un peu plus faible qu'avant, et qu'elle a mise au monde plus tard un enfant venu à terme.

Cas 3. Malade âgée de 38 ans; 7ième grossesse.

Admise à l'hôpital $^{13}/_{11}$ 1944—$^{10}/_{3}$ 1945.

Dernière menstruation mi-mai 1944. Cause de l'admission prolapsus génital. Elle n'avait pas eu d'hémorrhagie vaginale. Le fond de l'utérus tenait le milieu entre l'ombilic et le proc. xiphoide. Présentation de travers. Sur la lèvre postérieure du col utérin se trouvait une tumeur irrégulière de la grandeur d'une noix, saignante au toucher. Excision probatoire: carcinome.

Traitement: 2 fois à 10 jours d'intervalle émanation de radium (16 + 16 millicuries détr.) sur le col utérin. Le $^{16}/_{1}$ 1945 accouchement d'un enfant mort-né par version sur pied et extraction à cause de présentation de l'épaule et cordon prolabé. L'orifice utérin était complètement dilaté. Le $^{3}/_{2}$ le col utérin était tout normal, le corps utérin de forme, grandeur, position, consistance et mobilité normales, et il n'y avait rien d'anormal aux côtés.

La tumeur étant plus grande que dans les cas précédents on a institué une radiothérapie supplémentaire depuis le $^{4}/_{2}$. Toutefois une récidive s'est déclarée assez tôt, et l'état de la malade au mois de mai 1947 semble désolé.

Le résultat du traitement dans les deux premiers cas a donc été si satisfaisant qu'il me semble nécessaire de maintenir une certaine considération de la grossesse en cas du cancer du col utérin s'il s'agit d'une

grossesse avancée et quand le cancer peut être regardé comme étant en stade du début et ne dépasse pas les limites de l'utérus.

La distance entre le dépôt de radium et le fétus étant assez considérable une influence nuisible sur celui-ci ne semble pas à craindre. Je dois ajouter que les deux enfants se sont développés normalement.

En outre c'est un fait de très grand intérêt que l'accouchement s'est pu passer sans grande difficulté, surtout que l'orifice utérin s'est dilaté complètement, même que la période de dilatation a été assez prolongée.

Enfin on doit remarquer que les deux premières malades ont gardé leur menstruation et que l'une des malades a mise au monde un enfant plus tard, ce qui nous porte à croire que l'influence du radium sur les ovaires a été minime.

RÉSUMÉ

Rapport sur 3 cas de cancer du col utérin pendant grossesse avancée. Traitement purement local à l'émanation de radium. Accouchements sans grande difficulté. 2 des cas libres de récidive depuis 7 ans. Ces 2 malades ont gardé leur menstruation et l'une d'elles a accouchée une fois plus tard. Les enfants se sont développés normalement.

SUMMARY

Report on three cases of cancer of the cervix during advanced pregnancy. Exclusive local treatment with radium emanation. Parturitions without considerable difficulties. Two of the cases, under control, have not been presenting any recurrence for seven years. In both cases, menstruation did not cease, and, in one of them, another parturition occurred later on. Children developing normally.

ZUSAMMENFASSUNG

Bericht über 3 Fälle von Krebs des Cervix uteri bei vorgeschrittener Schwangerschaft. Nur lokale Behandlung mit Radiumemanation. Entbindung ohne grössere Schwierigkeiten. Zwei der Fälle sind seit 7 Jahren rezidivfrei. Diese 2 Patientinnen haben Ihre Menstruation behalten, und die eine hat später noch eine Entbindung durchgemacht. Die Kinder haben normale Entwicklung gezeigt.

FROM THE CARDIFF ROYAL INFIRMARY, CARDIFF, ENGLAND.

SOME COMPLICATING FACTORS IN THE RADIUM TREATMENT OF CARCINOMA OF THE CERVIX UTERI[1]

by

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The treatment of carcinoma of the cervix by radium can no longer be regarded as new therapy. On the contrary it has been practised for a sufficient number of years to permit of the publication from many centres of the results of treatment of large numbers of cases, and their follow-up for many years afterwards.

In the early days of this therapy the method of treatment, the dosage and the duration of the application were largely experimental and had to be determined to a certain extent by methods of trial and error. In this connection we owe much to the pioneer work of KELLY and BURNAM in America, LACASSAGNE and WICKHAM in France and FORSSELL and HEYMAN in Sweden; and it is HEYMAN whose work we are so glad to acknowledge and to appreciate in this publication.

In general it may be said that the earlier methods of therapy consisted in the insertion of a varying number of radium-charged needles of differing strength into the substance of the tumour and these methods were reviewed by the writer in 1929 (1). A certain degree of success was obtained by multiple radium needle puncture, but the undesirable feature of this method was traumatisation of the growth which was unavoidable. The essential feature of the FORSSELL-HEYMAN technique, however, lay in the avoidance of such traumatisation of the growth. Into the interior of the uterus, in cases in which the cervical canal can be found,

[1] Submitted for publication, June 7, 1947.

is inserted a tube containing 50 mgms of radium element appropriately screened, while to the vaginal aspect of the growth are applied 50 to 75 mgms of radium in a flat container or containers. The details, the technique, the frequency and the duration of these applications have been described in many publications and do not call for repetition in this paper.

HEYMAN's work was first brought to notice in Britain in 1924 (2) when he reported his results in 505 cases with 20.29 per cent. free of symptoms after five years. Later, in 1929 (3), his five year cure figure was 23.1 per cent. in 737 cases treated. In the Gynaecological Department of Cardiff Royal Infirmary and the Welsh National School of Medicine we have employed radium in the treatment of carcinoma of the cervix since 1922 and the Stockholm technique has been exclusively employed since 1930, while we have a consecutive record of some 1,400 cases. My colleague R. G. MALIPHANT (4) has just reported from our records a five year cure rate of 25.6 per cent. in 585 cases treated by this method up to 1941.

The main object of this communication, however, is not to discuss technique or even results, but to consider certain side-aspects of radium treatment of carcinoma of the cervix, particularly such conditions as would contra-indicate the application of radium and complications that may follow the application. It is obvious that factors of this nature would materially influence the ultimate results of treatment, so that they merit careful consideration.

Contraindications to Radium Therapy

Not every case of carcinoma of the cervix is suitable for the application, of at least the immediate application, of radium, and lack of appreciation of this fact, usually on account of insufficient investigation of the case or of lack of experience on the part of the surgeon, may markedly vitiate the result or may even precipitate disaster.

The following are the main conditions that, in our experience (5), contra-indicate the exhibition of radium in certain cases of carcinoma of the cervix.

(1) *Advanced emaciation and cachexia* — in such a case the growth itself is probably hopelessly advanced, while massive extensions may be present, so that it has to be regarded as untreatable, and even so slight an operation as radiotherapy may merely hasten the fatal result. Only fourteen cases in our series have come into this category. If, on the other hand, the poor general condition is due mainly to toxic absorption from a foul growth much improvement may result from rest, local cleansing and proper nourishment, so that, at a later date, it may be possible to

apply radium with great benefit, and we have seen many cases of this kind.

2) *Extensive anaemia* occurs usually from a combination of repeated haemorrhages and toxic absorption. We always observe the rule that with a red cell count of three millions or less and with 40 per cent. or less of haemoglobin radium should not be applied until these conditions have been improved by rest, nourishment and blood transfusion. Radium itself tends to produce a certain degree of anaemia and this, added to previous severe anaemia, may reduce the patient to a dangerous condition.

3) *Inflammatory pelvic lesions* should be cleared up, if this is possible, before radium is applied. The commonest of these lesions is a foul, sloughing condition of the growth and if radium be applied to a growth in this condition massive necrosis, together with parametritis or peritonitis, is likely to be set up. In a case of this sort, therefore, local cleansing by douching and the direct application of antiseptics should be carried out in order to clean up the condition before radium is applied.

Pyometra is less frequently encountered, but it is a deceptive condition and is often met with unexpectedly and unaccompanied by pyrexia or uterine enlargement. This emphasises the importance of finding and dilating the cervical canal, if this is at all possible, and in this connection we agree with HEYMAN that the external os is often to be found on the periphery of the growth and particularly on the right side. On cervical dilatation, if a pyometra is present, pus escapes from the interior of the uterus, often in surprising amount, and evacuation may be aided by a uterine douche which must be very gently administered without any pressure in order to avoid upward extension of the infection. The uterus should now be drained by the insertion of a rubber tube which has usually to be left in up to ten days, after which radium can be inserted.

Salpingitis, pyosalpinx or pelvic abscess are other inflammatory contra-indications to the immediate application of radium and they should receive appropriate treatment and be completely cured before radium is applied. Such treatment may be prolonged and may even involve surgical measures up to laparotomy for the removal of a pyosalpix, although the advent of the sulphonamides and of penicillin has shortened the time involved and has practically eliminated the necessity for active surgery. But these conditions may be very difficult to diagnose, even under anaesthesia, especially if they are associated with parametrial infiltration secondary to the cervical carcinoma.

4) *An extreme degree of pelvic extension* of the growth producing a plaster of Paris hardness would indicate an advanced state of stage IV of the disease and is usually accompanied by some of the other contra-indications previously discussed, such as cachexia or anaemia. In any

event a local remedy such as radium or even deep roentgen therapy is unlikely to be effective in the face of so widespread and formidable a condition. Indeed the strain of operation may do more harm than good, and, even if bleeding is controlled for a time by the radium, subsequent pelvic pain due to reactionary fibrosis is likely to be severe and distressing, so that at least a proportion of cases of this sort should be rejected as unsuitable for radiotherapy.

(5) *Fistula formation* is usually an indication of considerable extension of the growth and a sign that radium should not be applied. This is true especially of vesico-vaginal fistulae which are merely aggravated by the irritative effect of radium, but it will be shown that an occasional case of recto-vaginal fistula may be benefited by radium. These considerations bring to mind the importance of preventing fistula formation, as far as this is possible, by a proper technique of application and this will receive later consideration.

It will be noted that these contra-indications to radium therapy in cervical carcinoma are of two varieties. They may be temporary, as in the case of inflammatory conditions or anaemia, or permanent, as in extensive caking of the pelvis by growth. In the former case radium can be applied with safety after the complicating condition has been dealt with, but in the latter, radium should be withheld and the case rejected as unfit for this type of therapy. These considerations, and our subsequent consideration of the complications of radiotherapy, emphasise the importance of a thorough general and local examination of every case in which radium treatment is proposed, also the necessity for this therapy to be carried out by expert hands. Neglect of these measures may well lead to many of the complications that we consider later or even to disaster.

Technical Considerations during Radium Application

Much has been written regarding the technique of the Stockholm method of radiotherapy, so that further repetition is unnecessary and we wish to emphasise only two main points that we consider important.

The first of these concerns the finding of the cervical canal in order that it may be dilated and the intra-uterine tube of radium inserted, so that the involved cancer area may be irradiated to the best advantage. The difficulty in finding the canal has been referred to, also the frequency with which it may be demonstrated at some point in the periphery of the growth. In 28 per cent. of our cases the cervical canal could not be found. A prolonged attempt should be made to determine the cervical canal by the passage of a uterine sound or a small dilator, but this procedure must be carried out with the greatest of gentleness and care as

it may be unbelievably easy to perforate the soft growth unknowingly and so to set up pelvic inflammatory complications of any degree of gravity up to fatal peritonitis. As previously mentioned, the passage of the sound will in some cases demonstrate an unexpected pyometra.

When the cervical canal has been found it can usually be dilated with ease sufficiently to admit the intra-uterine radium tube, but if careful exploration entirely fails to demonstrate the cervical canal, the attempt has to be abandoned and only a flat or curved applicator or a bullet to the vaginal surface of the growth can be applied. In such a case, however, the risk of leaving an unsuspected pyometra has to be faced.

In some cases the cervical canal cannot be found at the first application but is easily identifiable on the second occasion, while in a smaller proportion of cases the reverse is the case.

The second technical point is the importance of efficient vaginal packing and this will be referred to in the next section.

Post-operative Complications of Radium Therapy

The proportion of cases in which the following complications of carcinoma of the cervix occur after radium therapy is small, and they may be directly due to the action of the radium, to faulty technique or to extension of the growth in spite of radium, and it is largely with the object of preventing these complications that we have emphasised the importance of the contra-indications to radiotherapy, of a careful investigation of the case and of efficient training of the surgeon.

In 1939 R. G. MALIPHANT (6) investigated this aspect of the matter in 650 consecutive cases treated in this department and some interesting considerations were brought to light.

Radium is an irritant to normal tissues and *irritation effects* may be encountered mainly in the adjacent bladder, rectum and vagina where cystitis, proctitis or vaginitis may occur. In order, as far as possible, to prevent these complications we always have the rectum thoroughly emptied before operation, while a self-retaining catheter is inserted into the bladder and is retained as long as the radium is *in situ*. But the most effective preventive of these complications is firm gauze packing of the fornices, and this not only retains the radium box in position against the growth at the vaginal vault but also separates the empty bladder and rectum as far as possible from the irritant action of the radium while the vagina is also shielded as far as possible. By observing these measures we have had very little experience of proctitis or cystitis although the former was frequently reported from many clinics as a troublesome sequel of radiotherapy in the early days of this treatment. Vaginitis will be discussed later in this paper.

Pelvic infection may be a troublesome, dangerous or even fatal complication of radium therapy. In MALIPHANT's analysis 12 deaths occurred and this represented 1.85 per cent. The causes of death were acute pyelonephritis (2), septicaemia (2) and peritonitis (8). These were all advanced cases and it would appear that this complication is predisposed to by the introduction of the uterine tube as in the cases in which the cervical canal could not be found the incidence of fatal infection was only one third of that when the intra-uterine tube was inserted. Again in 248 cases previously treated by the needling method the percentage of infective mortality was only 0.8 per cent. The danger of perforation when seeking for the cervical canal and the ease with which this may be brought about has previously been emphasised.

Post-operative *pyometra* occurred in 8 cases (1.23 per cent.) and again all these were advanced and, with one exception, over fifty years of age. The usual cause of this complication is fibrotic stricture at the isthmus and the condition would seem to be predisposed to by senile atrophy of the uterus. Just as in pre-operative pyometra the cervix has to be dilated, the pus evacuated and the condition drained, especially if further radiotherapy is indicated.

The importance of *fistulae* as contra-indications to radiotherapy has been noted and their occurrence after operation is well known. The main considerations in such a case are how far, if at all, has this complication been predisposed to by the application of radium and how much is it due to uncontrolled extension of the growth. In 1931 (7) we investigated this matter and found a post-operative incidence of 8.7 per cent. of fistulae in 254 cases. This represented 22 cases of which ten were vesico-vaginal, nine were recto-vaginal and three were recto-vesico-vaginal. It was, however, appreciated that with a longer follow-up of some of the more recent cases the proportion would probably be in the region of 10 per cent. MALIPHANT (6) in his later follow-up of 350 cases for five years or previous death found 20 recto-vaginal, 13 vesico-vaginal and 6 double fistulae, an all-in incidence of 11 per cent., while 80 per cent. of these occurred within three years of treatment. As fistula formation is an index of gravity of the condition, the prognosis in these cases is bad.

In some cases in which a rectal fistula is present and the disease has been cured repair may be attempted, and we have had success with this on one occasion, while GRAY WARD (8) has recorded two similar cases.

The majority of fistulae occurred in stage III cases and with an ulcerating type of growth. An important finding was that in 248 patients previously treated by interstitial radium the incidence of fistula formation was fully three times as high as when treatment was by HEYMAN's technique. The effect of re-radiation was also marked, and 23 out of

th 38 cases who developed fistulae received more than one course of ra iotherapy. This is what would be expected as re-radiation would in cate continued extension of the growth. The importance of technique in redisposing to fistula formation is demonstrated by the above figures, an , as progressive improvement occurs in this field, radium properly ap lied should in fact shield the patient from this complication.

Intestinal obstruction is an occasional late complication of cervical ca inoma but it is not necessarily influenced by the application of radium. It s usually due to the invasion of the sigmoid or rectum by the growth wh se extension has not been satisfactorily controlled by the radium, so hat it occurs in spite of radium. MALIPHANT found this complication in 8 out of 500 of our cases and in three of these it was terminal, so tha the patients did not long survive colostomy.

Stricture formation on account of fibrosis stimulated by the radium ma be a troublesome complication. This is seen most commonly at the vaginal vault and the resulting stenosis may render subsequent radiotherapy or even proper examination difficult. An occasional result of this complication is that the vaginal walls may become adherent below the growth, so that on examination an appearance of complete healing with a shortened vagina may be obtained, while the growth may actually be progressing above the vaginal occlusion. Vaginal stenosis in its incidence and degree is a very variable complication and the only means of prevention is a daily douche of a soapy preparation such as weak Lysol for six weeks after radium is applied. As regards treatment of the established condition this consists in digital dilatation and separation of the adhesions, but the probability of the re-formation of a fibrotic stricture is great.

Rectal and ureteric strictures have been described but we have no experience of them in our cases.

From what has been said it is evident that radiotherapy is associated with a definite *primary mortality* and this is usually quoted at from 1 to 4 per cent. In the Cardiff series MALIPHANT found a primary mortality of 2.6 per cent., representing 17 deaths of which 12 were due to acute infection as previously described, 1 was due to embolism and 4 to an odd type of general decline without obvious local cause even at post-mortem examination. An important point that emerges is that this entire mortality was encountered in advanced cases and, as previously mentioned, appeared to be predisposed to by the insertion of the uterine radium tube.

The consideration of these contra-indications to and the risks of radiotherapy emphasises the real dangers to which the woman with carcinoma, and especially with advanced carcinoma, of the cervix is exposed. It also indicates the importance of a thorough general and

local examination of the patient and the necessity for efficient training of the surgeon in the technique of radium application, while, as in all other branches of medicine, clinical judgment is paramount.

With improved technique many of these risks are being overcome, so that in the future the great pioneer work of James Heyman will continue to bear ever more and better fruit.

SUMMARY

Certain conditions are considered which should be regarded as contra-indications to the application of radium in some cases of carcinoma of the cervix. These are a very advanced condition of the disease, extensive anaemia, inflammatory pelvic lesions, cachexia and the presence of fistulae. During the application of radium the importance of finding the cervical canal, if this is possible, and of efficient vaginal packing is stressed.

Numerous post-operative complications such as infection, pyometra, fistula formation, instestinal obstruction and stricture formation are discussed, while the primary mortality rate is considered. Out of these considerations emerge the importance of a proper investigation of the case and of efficient training of the surgeon.

ZUSAMMENFASSUNG

Es werden gewisse Umstände besprochen, die als Kontraindikationen gegen die Anwendung von Radium bei gewissen Fällen von Zervixkrebs anzusehen sind. Diese sind weit vorgeschrittenes Stadium der Krankheit, starke Anämie, Entzündungen im Becken, Kachexie sowie Vorliegen von Fisteln. Bei der Einlegung von Radium wird die Wichtigkeit, wenn möglich den Zervixkanal zu finden, sowie eines genügenden Ausfüllens der Scheide betont. Zahlreiche postoperative Komplikationen, wie Infektion, Pyometra, Fistelbildungen, Darmverschluss und Strikturbildungen werden besprochen und die primäre Sterblichkeit in Betracht genommen. Aus diesen Erwägungen ergibt sich die Bedeutung einer sachgemässen Untersuchung des Falles und genügender Übung des Operateurs.

RÉSUMÉ

Certaines circonstances sont discutées qu'on devrait considérer comme des contre-indications à l'application du radium dans quelques cas de cancer du col. Ce sont: un degré très avancé de la maladie, une anémie sévère, des lésions pelviennes inflammatoires, la cachexie et la présence de fistules. L'auteur souligne l'importance, lors de l'application du radium, de trouver le canal cervical quand c'est possible, et celle d'un tamponnement efficace du vagin. Il discute de nombreuses complications post-opératoires, telles que l'infection, la formation de fistules, l'obstruction intestinale et l'apparition de rétrécissements. De ces considérations ressort l'importance d'un examen adéquat du cas et d'une éducation suffisante du chirurgien.

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SUMMARY OF RESULTS IN THE RADIATION TREATMENT OF UTERINE CERVICAL CANCER[1]

A Statistical Study of Volume 4 of the League of Nations »Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix», edited by Prof. J. Heyman, Statement of 5 Year End-Results of 1,796 Patients whose Treatment Began in 1933.

By

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I am honored to be invited to join with other medical colleagues to honor Prof. JAMES HEYMAN in celebration of his sixty-fifth birthday. Having spent several weeks in attendance at his Gynecologic Clinic at the Radiumhemmet in Stockholm, I have never ceased in my admiration of him as a clinical teacher. Surely every gynecologist and radiologist is forever indebted to Prof. HEYMAN for the years of labor he devoted to the »Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix», published four years prior to World War II by the League of Nation's Health Organization under his editorship. These splendid reports are the best statistical studies that have been compiled in the study of the end-results of the radiologic treatment of uterine cervical cancer. It is the purpose of this paper to summarize the five year end-results of the last published report (Volume 4) which was printed in 1941.[2] This covered the patients first treated in 1933 and of course the end-results five years later. The report was compiled in 1939 but because of the onset of World War II publication was not completed until 1941. As a result of World War II it would seem almost certain that statistical studies from a number of the institutions re-

[1] Submitted for publication, May 10, 1947.

[2] Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix. Fourth Volume. Statement of Results Obtained in 1933 and Previous Years. Edited by J. HEYMAN, M. D. League of Nations Health Organization. P. A. Norstedt & Söner. Stockholm, 1941.

porting to the League of Nations will not be available for some years. The heavy civilian casualties in most of the reporting nations will effect the accuracy of this splendid statistical study in future reports for the years immediately preceding the war as well as the war years themselves. The author, in 1940, compiled a summary of HEYMAN's statistical studies for the League of Nations group for the year of 1932 comprising 1,431 cases of uterine cervical cancer treated by radiotherapy in 16 radiotherapeutic centers in 7 countries.[1]

In the final analysis of the 1932 series it was shown that the best results were obtained at the Radium Institute of the University of Paris where 51.5 percent of all patients treated (101 cases) were alive and free from cancer at the end of five years. A break-down study of the various stages gave the following conclusions:

»The best results (considering only institutions where 100 or more patients were treated during the year) in the treatment of Stage I growths — 85.7 percent five-year survivals, were at the Marie Curie Hospital in London; the best results in Stage 2 — 53.5 percent, Stage 3 — 41.2 percent, and Stage 4 — 16.7 percent, were at the Radium Institute of the University of Paris.»[2]

Inasmuch as the present study is an analysis of the results in the League of Nations' institutions for the year 1933, the following is quoted from our 1940 study as it applies equally well to the present study:[1]

»Here for the first time are recorded the important statistical data pertaining to the disease (uterine cervical cancer) from a group of the leading cancer clinics throughout the world. The interesting point pertaining to this group is that all of the patients are classified in a uniform manner so that the stage of the disease treated in each clinic is apparent. The patients have been grouped in four stages, as found at the beginning of the treatment, in accordance with the League of Nations classification in 1929 (based on the results of the gynecologic findings) and the end-results of the radiation therapy recorded.»

Stages of Uterine Cervical Cancer

»Stage I. (Operable) The growth is strictly limited to the cervix uteri. Uterus mobile.

»Stage II. (Doubtful operable) Lesion spreading into one or more fornices, with or without infiltration of the parametrium adjacent to the uterus, the uterus retaining some degree of mobility.

[1] SWANBERG, HAROLD: Results of Radiation Therapy in Uterine Cervical Cancer (1932). Mississippi Valley Medical Journal, 62: 54—61, March 1940.

[2] Id.

»Stage III. (Inoperable) (a) Nodular infiltration of the parametria on one or both sides extending to the wall of the pelvis, with limited mobility of the uterus or massive infiltration of one parametrium with fixation of the uterus. (b) More or less superficial infiltration of a large part of the vagina, with a mobile uterus. (c) Isolated metastases in the pelvic glands, with a relatively small primary growth. (d) Isolated metastases in the lower part of the vagina. Generally speaking all cases not falling into Stages II or IV will be placed under Stage III.

»Stage IV. (Inoperable; Terminal) (a) Cases with massive infiltration of both parametria extending to the walls of the pelvis. (b) Carcinoma involving the bladder or rectum. (c) The whole vagina infiltrated (rigid vaginal passage), or one vaginal wall infiltrated along its whole length, with fixation of the primary growth. (d) Remote metastases.

»The new 1937 League of Nations Classification of the four clinical stages of uterine cervical cancer, which is to be used henceforth, is as follows:

»Stage I. The carcinoma is strictly confined to the cervix.

»Stage II. The carcinoma infiltrates the parametrium on one or both sides, but has not invaded the pelvic wall ... Stage II, parametrium. The carcinoma infiltrates the vagina, but does not involve its lower third ... Stage II, vagina. Endocervical carcinoma which has spread to the corpus ... Stage II, corpus.

»Stage III. The carcinomatous infiltration of the parametrium has invaded the pelvic wall on one or both sides. On rectal examination no cancer-free space is found between the tumor and the pelvic wall ... Stage III, parametrium. The carcinoma involves the lower third of the vagina ... Stage III, vagina. Isolated carcinomatous metastases are palpable on the pelvic wall (irrespective of the extent of the primary cervical growth) ... Stage III, isolated pelvic metastases.

»Stage IV. The carcinoma involves the bladder as determined by cystoscopic examination or by the presence of a vesico-vaginal fistula ... Stage IV, bladder. The carcinoma involves the rectum ... Stage IV, rectum. The carcinoma has spread outside the true pelvis (below the vaginal inlet, above the pelvic brim, distant metastases) ... Stage IV, distant spread.

»General rule to be observed: When allocating a case to a stage, nothing but facts revealed by examination should be taken into account. The stage of each case should be decided at examination prior to treatment, and this classification should remain. The classification may be postponed quite exceptionally and the reasons stated. When it is doubtful to which stage a given case is to be allocated, the earlier stage should be chosen. The fact that single case present two or more of the conditions which characterize a particular stage does not effect the staging.«

Table 1.

Institution	Director	Year of report	Number of patients treated	Percentage of each stage				Patients alive without evidence of cancer end of 5 years	Relative 5-year cure rate
				1	2	3	4		
A Memorial Hospital, N. Y. City	Wm. P. Healy	1933	124	8.1 %	8.9 %	60.5 %	22.6 %	33	26.6 %
B State Institute, Buffalo, N. Y.	B. F. Schreiner ..	1933	179	5.0 »	18.4 »	48.6 »	27.9 »	65	36.3 »
C Women's Hospital, N. Y. City	George G. Ward ...	1933	29	24.1 »	55.2 »	17.2 »	3.4 »	8	27.6 »
D Center for Tumors, Brussels	Prof. J. Murdoch .	1933	94	26.6 »	26.6 »	36.2 »	10.6 »	16	17.0 »
E Inst. for Cancer, Louvain	Prof. J. Maisin ...	1933	61	1.6 »	37.7 »	54.1 »	6.6 »	21	34.4 »
F General Infirmary, Leeds	A. A. D. La Touche	1933	93	2.2 »	38.7 »	38.7 »	20.4 »	22	23.7 »
G Holt Rad. Inst., Manchester	Ralston Paterson	1933	113	6.2 »	34.5 »	38.0 »	21.2 »	35	31.0 »
H Liverpool Radium Inst. .	P. Malpas	1933	70	5.7 »	41.4 »	37.1 »	15.7 »	14	20.0 »
I Marie Curie Hosp., London	M. W. Gilmour...	1933	101	4.0 »	27.7 »	53.5 »	14.9 »	38	37.6 »
J Ra. Center for Wales, Cardiff	G. I. Strachan ...	1933	58	25.9 »	32.8 »	36.2 »	5.2 »	11	19.0 »
K Radium Station, Copenhagen	O. Chiewitz	1933	231	9.1 »	39.8 »	35.9 »	15.2 »	74	32.0 »
L Radium Stadion, Aarhus	C. Krebs	1933	97	27.8 »	28.9 »	26.8 »	16.5 »	27	27.8 »
M Institute for Cancer, Paris	Simone Laborde ..	1933	68	2.9 »	7.4 »	54.4 »	35.3 »	16	23.5 »
N Institute for Radium, Paris	A. Lacassagne....	1933	125	12.8 »	36.0 »	40.0 »	11.2 »	59	47.2 »
O Amsterdam	D. den Hoed	1933	47	10.6 »	29.8 »	53.2 »	6.4 »	16	34.0 »
P Norse Radium Hospital, Aker	E. Schjott-Rivers	1933	102	24.5 »	27.5 »	36.3 »	11.8 »	37	36.3 »
Q Radiologic Clinic, Gothenburg	F. von Bergen ...	1933	40	37.5 »	27.5 »	30.0 »	5.0 »	18	45.0 »
R Radiumhemmet, Stockholm	Prof. J. Heyman ..	1933	164	7.9 »	41.5 »	32.9 »	17.7 »	42	25.6 »
	Grand Total		1,796	11.6 %	30.6 %	41.1 %	16.7 %	552	30.7 %

The names of the 18 reporting institutions, the number of patients radiologically treated by each during 1933 for uterine cervical cancer, the percentage of patients for each of the four clinical stages and the relative 5-year survival rate.

Statistical Analysis

This study comprises all the patients (1,796) suffering from uterine cervix cancer treated at the 18 reporting radio-therapeutic centers in 8 countries beginning in 1933, observing the effects of the treatment at the end of five years. Irradiation therapy was used exclusively. All patients had microscopic proof of the disease, and all patients lost track of, or who died from intercurrent disease, during the five-year interval, from the time the treatment was started, were considered cancer deaths.

Table 2.

Institution	Stage 1			Stage 2			Stage 3			Stage 4		
	Number of patients treated	Alive without evidence of cancer	Relative 5-year cure rate	Number of patients treated	Alive without evidence of cancer	Relative 5-year cure rate	Number of patients treated	Alive without evidence of cancer	Relative 5-year cure rate	Number of patients treated	Alive without evidence of cancer	Relative 5-year cure rate
A Memorial Hospital, New York City	10	6	60.0 %	11	3	27.3 %	75	24	32.0 %	28	0	0.0 %
B State Institute, Buffalo, N. Y.	9	5	55.6 »	33	19	57.6 »	87	40	46.0 »	50	1	2.0 »
C Woman's Hospital, New York City	7	3	42.9 »	16	5	31.3 »	5	0	†	1	0	†
D Center for Tumors, Brussels	25	12	48.0 »	25	1	4.0 »	34	3	8.8 »	10	0	0.0 »
E Institute for Cancer, Louvain	1	1	†	23	13	56.5 »	33	7	21.2 »	4	0	†
F General Infirmary, Leeds	2	0	†	36	15	41.7 »	36	7	19.4 »	19	0	0.0 »
G Holt Radium Institute, Manchester	7	5	71.4 »	39	18	46.2 »	43	10	23.3 »	24	2	8.3 »
H Liverpool Radium Institute	4	2	†	29	9	31.0 »	26	3	11.5 »	11	0	0.0 »
I Marie Curie Hospital, London.	4	3	†	28	18	64.3 »	54	16	29.3 »	15	1	6.7 »
J Radium Center for Wales, Cardiff	15	4	26.7 »	19	3	15.8 »	21	4	19.0 »	3	0	†
K Radium Station, Copenhagen	21	14	66.7 »	92	37	40.2 »	83	20	24.1 »	35	3	8.6 »
L Radium Station, Aarhus	27	11	40.7 »	28	12	42.9 »	26	3	11.5 »	16	1	6.3 »
M Institute for Cancer, Paris	2	1	†	5	2	†	37	10	27.0 »	24	3	12.5 »
N Institute for Radium, Paris	16	13	86.7 »	45	23	51.1 »	50	20	40.0 »	14	3	21.4 »
O Amsterdam	5	4	†	14	4	28.6 »	25	8	32.0 »	3	0	†
P Norse Radium Hospital, Aker.	25	13	52.0 »	28	16	57.1 »	37	7	18.9 »	12	1	8.3 »
Q Radiologic Clinic, Gothenburg.	15	11	73.3 »	11	5	45.5 »	12	2	16.7 »	2	0	†
R Radiumhemmet, Stockholm	13	9	69.2 »	68	21	30.9 »	54	11	24.4 »	29	1	3.4 »
Grand Total	208	117	56.2 %	550	224	40.7 %	738	195	26.4 %	300	16	5.3 %

† Too few cases to warrant a statement of percentage.

The names of the 18 reporting institutions, the number of patients radiologically treated during 1933 for each of the four clinical stages of uterine cervical cancer, together with the relative five-year survival rate. (Dr. M. D. Gilmour, Director of the Marie Curie Hospital of London, has, in a personal communication to the author, supplied the missing figures, for that institution, in the Fourth Volume of the League of Nations report.)

To be considered a five-year survivor the patient has to be alive and free from cancer, as revealed by a careful clinical examination.

The tables given in the text are self-explanatory giving the number of patients treated at each institution, together with the end-results for each clinical stage, etc.

In reviewing the tables it will be noted that the number treated at each radiotherapeutic center showed a wide variation from a low of 29 to a high of 231. At some of the smaller centers only one, two or three Stage 1 or Stage 4 patients were treated; with these small numbers one institution had a 100 % end-result in their Stage 1 patients. It is well

Table 3.

	Number of patients treated	Percentage of each stage	Alive without evidence of cancer	Relative 5-year rate cure
Stage 1	208	11.6 %	117	56.2 %
Stage 2	550	30.6 »	224	40.7 »
Stage 3	738	41.1 »	195	26.4 »
Stage 4	300	16.7 »	16	5.3 »
Grand total	1,796	100 %	552	30.7 %

Summary of the number of patients radiologically treated for uterine cervical cancer during 1933 at the 18 reporting institutions, the percentage for each of the four clinical stages and the relative five-year cures per clinical stage.

recognized that for proper statistical evaluation studies of small groups are not reliable. Therefore we have not recorded a percentage for any stage if less than seven patients were treated and for final evaluation we have set an arbitrary figure of at least 100 patients from any single radiotherapeutic center as a minimum.

With the above standards as a guide the best results in the Stage 1 group were secured at the Radium Institute of the University of Paris — 86.7 %, with the Radiologic Clinic at Gothenburg, Sweden, second with 73.3 %; for Stage 2 the Marie Curie Hospital of London heads the list with 64.3 % and the State Institute for the Study of Malignant Diseases, Buffalo, New York, is second with 57.6 %; for Stage 3 the State Institute for the Study of Malignant Diseases is first with 46 % and the Radium Institute of the University of Paris second with 40 %; for Stage 4 the University of Paris again heads the list with 21.4 % and the Institute for Radium of Paris is second with 12.5 %.

The final figures or all stages gives first place to the Radium Institute of the University of Paris with a five-year survival figure of 47.2 % which heads the entire list of 18 radiotherapeutic centers regardless of the number of patients treated per center. Considering only institutions treating over 100 patients for the year, second place goes to the Marie Curie Hospital of London with a 37.6 % survival rate; the State Institute for the Study of Malignant Diseases, Buffalo, New York, and the Norse Radium Hospital, Aker, Norway, are tied for third place with a 36.3 % survival rate.

Table 3 gives the total percentage of each stage of the disease for the 1,796 patients who were treated in 1933. If Stages 1 and 2 are considered »early cases», they comprised 42 %; and if Stages 3 and 4 are considered »advanced cases», they comprised 58 % of the patients. This table reveals

Table 4.

Treatment	Institution	Number of patients treated	% 5 years cures stages 1 & 2	% 5 years cures stage 3 & 4	Number of patients without cancer after 5 years
Radiation	Radium Institute, Paris	100	60.9 % (26)	34.6 % (20)	46
»	State Institute, Buffalo, N.Y.	100	57.1 » (24)	32.7 » (19)	43
»	Marie Curie Hospital, London	100	67.2 » (28)	22.4 » (13)	41
»	Norse Radium Hospital, Aker, Norway	100	55.7 » (24)	15.8 » (9)	33
»	Holt Radium Institute, Manchester	100	53.1 » (22)	19 » (11)	33
»	Radium Station, Copenhagen	100	45.1 » (19)	19.7 » (11)	30
»	Radiumhemmet, Stockholm .	100	43.8 » (18)	18.2 » (11)	29
»	Memorial Hospital, New York	100	36.3 » (15)	22.5 » (13)	28

Expected results in the respective large radiotherapeutic centers for 100 consecutive patients suffering from ALL stages of uterine cervical cancer in the proportions shown in Table 3.

the pathetic story about uterine cervical cancer, viz. over 50 % of the patients have advanced lesions when the treatment is begun.

Table 4 gives the probable five year end-results for the 8 radiotherapeutic centers, where 100 or more patients are treated during the year, if each institution treated the same percentage of each stage of the disease as shown in Table 3. This is the only accurate way of making a comparative study, because an institution may have a relatively high percentage of cures for the simple reason that few advanced cases are treated.

If 100 consecutive patients suffering from uterine cervical cancer were treated at the Radium Institute of the University of Paris, where the best results are reported, all stages of the disease would probably be treated by combined internal and external radiation. Based on the 1933 results, we could expect a total of 46 alive and free from cancer at the end of five years. If the percentage of the various stages of the disease were as shown in Table 4, 60.9 % of the early growths (Stage 1 and 2) and 34.6 % of the advanced lesions (Stage 3 and 4) should be cured. At the State Institute for the Study of Malignant Diseases, Buffalo, New York, 43 would be alive and free from cancer at the end of five years — 57.1 % of the early growths and 32.7 % of the advanced lesions; at the Marie Curie Hospital of London, 41 would be alive and free from cancer at the end of five years — 67.2 % of the early growths and 22.4 % of the advanced lesions; at the Norge Radium Hospital, Aker, Norway, 33 would be alive and free from cancer at the end of five years — 55.7 % of the early growths and 15.8 % of the advanced lesions etc.

Radiation Technique

The radiation technique used to secure the excellent results reported at the Radium Institute of the University of Paris was published in our 1939 studies of the League of Nations institutions.[1] This consisted of combined internal and external irradiation (internal radium alone in Stage 1). The internal radium treatment consisted of multiple (usually 6) small milligram centers of heavily filtered radium (1 to 1.5 mm of platinum) distributed throughout the entire length of the uterine canal and width of the vaginal vault, slowly administered (5 days' time) averaging 8,000 milligram hours.

The radiation technique used to secure the very good results reported at the Marie Curie Hospital of London was also published in our 1939 studies of the League of Nations Institutions.[1] Only a comparatively few patients received combined internal and external radiation. All received internal radium with three treatments (within 3—4 weeks) of heavily filtered radium (1 to 1.3 mm of platinum) distributed throughout the entire length of the uterine canal and width of the vaginal vault, for a total of 7,200—7,800 milligram hours, more rapidly administered than at Paris.

A personal communication from SCHREINER of the State Institute for the Study of Malignant Diseases, Buffalo, N. Y., reveals that combined internal and external irradiation was used there in 1933. The internal radium treatments consisted of large amounts of heavily filtered radium (50—100 mg) placed in the lower uterine segment for a short period (2,400 milligram hours) and 0.3 mm gold seed implants planted in the cervix and fornices for 1,200 to 1,800 mc hours. SCHREINER states: »It is only fair to state that with the concentrated treatment as given from 4 days to 2—3 weeks we had a great deal of late radium manifestations in the bladder and rectum and that we had to retreat patients in from 30 %—40 % especially in the Grade II and III. It is for this reason that this method of treatment has been abandoned and weaker tubes of radium substituted extending over long periods of time supplemented with larger amounts of external irradiation.» SCHREINER states (Dec. 1941) that in recent years they have handled their cases first with intensive external irradiation »followed with radium treatment according to the Lacassagne-Regaud idea (Radium Institute of University of Paris), where possible, one to four weeks later. Total amount of radium, 10, to 15 milligram cells, three in the uterus, colpostat one tube each end, and two tubes across the end of the intra-uterine applicator, for total of 4,000 to 6,000 milligram hours of radium. There has been surprisingly little bladder

[1] TWANBERG, HAROLD: »What Radiation Technic gives the best Clinical Results in Uterine Cervical Cancer?», Mississippi Valley Medical Journal, 61: 57—65, March 1939.

and rectal irritation as a result of this treatment.» Thus we see that the Buffalo institution practically adopted the Radium Institute of Paris technique of internal radium therapy.

Surgery Versus Radiation

It is difficult to make a comparative study of the best surgical and the best radiologic results in this disease. For years the 40 % five year cures as reported at the Wiebel Clinic in Vienna for the radical Wertheim panhysterectomy was considered about the most that could be expected. The operation, unfortunately, has been associated with a comparatively high primary mortality which has been prohibitive in the hands of the average sugeon. In recent years, with the introduction of modern chemotherapy and antibiotics, the primary operative mortality in the hands of a few skilled gynecologic surgeons has been materially reduced. MEIGS of Boston has been championing a return to the surgical treatment of the disease but the average general surgeon cannot hope to duplicate his results.

Unfortunately, the »early cases», Stage 1 and 2, are the only ones in which the surgical treatment can be considered, and they only comprise 42 % of the patients. All will admit that in the »advanced cases», Stage 3 and 4, the surgical treatment cannot be even considered and they comprise 58 % of the patients. If the average surgeon, with the modern use of antibiotics, could duplicate the results of the Wiebel Clinic, the radiation treatment of all stages of the disease would still easily be the best therapy.

Main Results

1. A statistical study of 1,796 treated patients, in 18 well-known radiotherapeutic centers in 8 countries, suffering from all stages of cancer of the uterine cervix, microscopically confirmed and treated exclusively by radiation therapy beginning in 1933, is analysed as to the end-results 5 years later.

2. It is shown that 11.6 % were Stage 1 growths, 30.6 % Stage 2, 41.1 % Stage 3 and 16.7 % Stage 4 with a relative curability of 30.7 % for the entire series.

3. The best results (considering only institutions where 100 or more patients were treated during the year) in the treatment of Stage 1 growths — 86.7 % and Stage 4 — 21.4 % five-year survivals, were at the Radium Institute of the University of Paris; the best results in Stage 2 lesions — 57.6 %, were at the Marie Curie Hospital of London, and Stage 3 growths — 46 % at the State Institute for the Study of Malignant Diseases, Buffalo, New York.

4. The conclusion is reached that the best results in all 18 radiotherapeutic centers, regardless of the number of patients treated, were secured at the Radium Institute of the University of Paris where 47.2 % of all patients treated were alive and free from cancer at the end of five years.

5. The radiation technique pursued to secure these excellent results at Paris consisted of combined internal (intra cavitary) and external (transpelvic) irradiation (internal radium alone in Stage 1); the internal radium treatment consisted of multiple, small milligram centers of heavily filtered radium distributed throughout the entire length of the uterine canal and width of the vaginal vault, slowly administered (5 days time) averaging 8,000 milligram hours.

6. In the hands of a few, highly skilled gynecologic surgeons, good results, with a lower primary mortality due to the introduction of chemotherapy and antibiotics, have been reported in recent years following the radical surgical treatment in »early cases» who were good operable risks. The radiation treatment, however, still remains the best therapy for the great majority of sufferers.

SUMMARY

The author summarizes the five year endresults of the last volume (IV) of »The Annual Report on the Results of Radio-therapy in Cancer of the Uterine Cervix», published by the League of Nations Health Organization under the editorship of Professor JAMES HEYMAN. He finds that every gynecologist and radiologist is for ever indebted to professor HEYMAN for the years of labour he devoted to these reports.

ZUSAMMENFASSUNG

Verf. macht eine Zusammenfassung der fünfjährigen Resultate im letzten Bande (IV) des »The Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix» (Jahresbericht der Ergebnisse der Radiotherapie bei Krebs des Cervix uteri), der unter Schriftführung von Professor JAMES HEYMAN von der Gesundheitsorganisation des Völkerbundes herausgegeben wurde. Er findet, dass jeder Gynäkologe und Radiologe Professor HEYMAN für die Jahre von Arbeit, die er diesen Berichten gewidmet hat, auf alle Zeiten Dank schuldet.

RÉSUMÉ

L'auteur résume les résultats finals après cinq ans rapportés dans le dernier volume (IV) du »Rapport annuel des résultats de la Radiothérapie du Cancer du Col utérin» publié par l'Organisme sanitaire de la Société des Nations, sous la direction du Professeur JAMES HEYMAN. Il estime que gynécologues et radiologues sans exception ont contracté une dette imprescriptible envers le Professeur HEYMAN pour les années de travail qu'il a consacrées à ces rapports.

FROM THE HOLT RADIUM INSTITUTE, MANCHESTER, ENGLAND

OPTIMUM DOSAGE IN THE TREATMENT OF CANCER OF THE CERVIX BY RADIATION[1]

by

Margaret C. Tod, F.R.C.S.E., F.F.R.

In January 1941 I published in the British Journal of Radiology a short paper (I) on optimum dosage in the treatment of cancer of the uterine cervix by radiation. In that paper the doses for 370 out of a total of 527 cases treated at the Holt Radium Institute during the five years 1932 to 1936 were calculated and »spot» graphs were drawn to try to find the dose in relation to time which produced the best results. The conclusion arrived at was that the following would probably prove to be optimum dose levels:

7,500 to 8,500 in 6 to 7 days radium only.

8,500 to 9,500 in 3 or 4 serial weekly applications radium only.

9,500 to 10,500 summated dose at point A for combined radium plus rontgen treatment in 4 to 6 weeks overall time.

In 1944 STRANDQUIST (2) published a thesis on radiation effects in relation to dose and time using as his material 280 cases of cancer of the skin and lip treated at the Radiumhemmet. He made ingenious use of the »spot graph» method showing only failures and high dose effects and obtained some interesting curves. The study now undertaken of the effect of dose and time in the treatment of cancer of the cervix does not, however, lend itself to this method of presentation. The large number of cases treated to precalculated dosage bring together large groups at single points so although the »spot» method was used as an important first step, the effects of dose and time are shown by the percentage of patients symptom-free at 3 years. The groups of cases were treated with doses of gamma and Roentgen rays varying from 5,000 r to 12,000 r in periods of one to six weeks.

[1] Submitted for publication, June 3, 1947.

Material

During the eleven years under survey the total number of cases of carcinoma of the uterine cervix which were given some form of radiotherapy was 2,331. This includes the material which I used for my first paper. Table 1 shows the net survival rate at three and at five years.

Table I.

Total cases treated 1932—1943 stage 1, 2, 3 and 4.

Total at 3 years — 2,331. Total at 5 years 1,754.

	1932	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	1943
Total treated	92	113	173	159	145	153	178	129	256	356	251	326
% Survival at 3 years	31 %	40 %	36 %	26 %	35 %	39 %	41 %	38 %	38 %	45 %	45 %	49 %
% Survival at 5 years	23 %	33 %	32 %	21 %	26 %	30 %	32 %	31 %	30 %	39 %		

This table shows all cases including those given purely palliative treatment. The survival rates are net figures after the withdrawal of cases which died of intercurrent disease (40 cases) or remained untraced (20 cases). It does not include any cases with a pathological report of adenocarcinoma. It is not possible to use every case for a study of this kind and the first to be discarded are cases in stage 4 and all earlier cases in which treatment was incomplete. This leaves only cases in stages 1, 2 and 3 completely treated — 1,601 cases in all. The old League of Nations staging is used. There is no particular reason for taking results at five years and as three years was taken in my first paper to get enough cases the third anniversary has been used again. The second table shows the three year percentage survival rate by stage for all cases completely treated for 1932—1943 omitting stage 4.

Table II.

	Complete + Roentgen		Complete — no Roentgen		Total Completely Treated	
	Number Treated	% 3 year survival	Number Treated	% 3 year survival	Number Treated	% 3 year survival
Stage I	23	65 %	100	88 %	123	83 %
» II	264	53 %	618	59 %	882	57 %
» III	265	39 %	331	37 %	596	38 %
Total	552	47 %	1 049	54 %	1,601	51 %

From the total of 1,601 cases a further deduction must be made:

Total cases in stage 1, 2 and 3 completely treated		1,601
Already discarded when years 1932—1936 were assessed	40	
Stump carcinoma	23	
Not confirmed by pathological examination	12	
Not symptom-free at 3rd anniversary but not yet known to be diseased (cases treated in 1942 and 1943)	13	88
Total cases for survey		1,513

Technique of Treatment

It is necessary before discussing the effects of varying dose and time to describe the techniques used, because the method of irradiating and the interval between treatments so influences the biological reaction that results are only valid in relation to the particular pattern of time intensity and interval which is used. The main division is between those cases treated with Radium alone and those treated by a combination of Radium and roentgen.

The cases treated by *Radium alone* fall into the main groups:

A. 1. 2 applications of 72 hours each, interval one day, overall time seven days.

A. 2. The same as A. 1 but with an interval of four days, overall time ten days.

A. 3. Three or four Radium applications of 48 hours each given in an overall period of about three weeks. This method was considerably varied at different times and was occasionally completed in 16 days but on the other hand was sometimes extended to 24 days.

This A 3 arrangement was used for a small number of cases treated by Radium alone in 1933 and 1934 and again in 1937. In 1938 and 1939 it was slightly modified because dose was then precalculated and, although the duration of individual applications might vary, the dose and the overall time of treatment were kept constant.

The A 1 arrangement was used for the small number of cases treated by radium alone in 1935 and 1936. When the survival rates for these years were examined in 1939 it was found that the few cases treated had done well enough to justify a decision to reduce the time of treatment to approximately one week of continuous irradiation. The technique was, therefore, again employed because it was expedient in the conditions of the first year of the war period. It proved so satisfactory that it is still the method used for treatment by Radium alone, the only modification being an increase of the interval from one to four days. (A 2)

Treatment by Radium combined with roentgen falls into three groups:

1. Large field roentgen therapy to the whole pelvis followed immediately by a continuous radium application of 6 to 7 days. Overall time four weeks. The proportion of the dose obtained from external roentgen radiation was 30 %.

2. Three or four radium applications of 48 hours each with large field roentgen therapy to the whole pelvis given after the first two, and before the third, radium applications. Overall time five to six weeks according to the number of radium applications. Approximately 25 % of the dose was obtained from the external roentgen radiation.

3. Radium insertion to deliver a precalculated dose in three applications of 48 hours each with a course of small field beam-directed therapy to the parametria between the first two and the last radium application. Overall time five to six weeks according to length of roentgen treatment. The proportion of the dose obtained from external roentgen radiation varied from 30—35 %.

In addition to these three main groups a small number of patients was treated during the war years by two radium applications followed by a four days course of small field beam-directed roentgen therapy to the parametria.

A modification of method B. 3. is that now in use for the combined treatment of cases with wide-spread involvement of the parametria. Two Radium applications of 72 hours are used with 24 days of roentgen therapy between the radium applications — overall time five weeks.

These techniques will be referred to by the number *i. e.* A. 1, B. 1 etc. on the table and graph.

Dosage

The method of precalculating the dose makes use of the units system which, in collaboration with W. J. MEREDITH, I described in 1938 (3).

Special applicators, named ovoids, together with an intrauterine tube are loaded with specified units of radium arranged in a definite order. The number of units varies with the size of applicators which the vagina will admit, the range of width at the level of the external os varying from two to ten centimetres. Dose is calculated at a point in the paracervical triangle which has been defined and designated point A. It is 2 cms. lateral to the central canal of the uterus and 2 cms. from the mucous membrane of the lateral fornix in the axis of the uterus. The use of the units system ensures that the dose from uterine tube and vaginal

From the total of 1,601 cases a further deduction must be made:

Total cases in stage 1, 2 and 3 completely treated		1,6
Already discarded when years 1932—1936 were assessed	40	
Stump carcinoma	23	
Not confirmed by pathological examination	12	
Not symptom-free at 3rd anniversary but not yet known to be diseased (cases treated in 1942 and 1943)	13	3
Total cases for survey		1,5 3

Technique of Treatment

It is necessary before discussing the effects of varying dose and time to describe the techniques used, because the method of irradiating and the interval between treatments so influences the biological reaction that results are only valid in relation to the particular pattern of time intensity and interval which is used. The main division is between those cases treated with Radium alone and those treated by a combination of Radium and roentgen.

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A. 1. 2 applications of 72 hours each, interval one day, overall time seven days.

A. 2. The same as A. 1 but with an interval of four days, overall time ten days.

A. 3. Three or four Radium applications of 48 hours each given in an overall period of about three weeks. This method was considerably varied at different times and was occasionally completed in 16 days but on the other hand was sometimes extended to 24 days.

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B 1. Large field roentgen therapy to the whole pelvis followed immediately by a continuous radium application of 6 to 7 days. Overall time four weeks. The proportion of the dose obtained from external roentgen radiation was 30 %.

B 2. Three or four radium applications of 48 hours each with large field roentgen therapy to the whole pelvis given after the first two, and before the third, radium applications. Overall time five to six weeks according to the number of radium applications. Approximately 25 % of the dose was obtained from the external roentgen radiation.

B. 3. Radium insertion to deliver a precalculated dose in three applications of 48 hours each with a course of small field beam-directed therapy to the parametria between the first two and the last radium application. Overall time five to six weeks according to length of roentgen treatment. The proportion of the dose obtained from external roentgen radiation varied from 30—35 %.

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applicators is balanced and that the dosage rate remains the same at point A regardless of the size of applicators used.

In this series of cases the range of dosage at point A available for assessment is from 6,000 to 12,000 r. The volume of tissue treated varies slightly with Radium alone because the large ovoid which carries the highest number of units to balance the dose at point A must necessarily deliver a slightly higher depth dose. As soon as roentgen therapy is added the volume of tissue treated is greatly increased and the effect of the combined dosage, particularly when large fields include the whole pelvis, is very different from that produced by the localised irradiation of intracavitary radium.

Table III.

Table showing numbers used for graph.

Overall time of treatment	Dose	Number assessed	Number well	Number dead or diseased	% well	High dose effect Number of cases		High dose effect %
						Alive	Dead	
1 week	5,000 r	3	0	3	0 %	—	—	—
	6,000 r	22	4	18	22 %	—	—	—
A. 1	6,500 r	27	13	14	48 %	—	—	—
	7,000 r	161	61	100	38 %	2	0	1 %
	8,000 r	146	93	53	64 %	2	2	3 %
	9,000 r	207	98	109	47 %	11	15	13 %
10 days	6,000 r	4	0	4	0 %	—	—	—
	6,500 r	7	3	4	43 %	—	—	—
A. 2	7,000 r	104	70	34	67 %	0	2	2 %
	8,000 r	189	103	86	55 %	1	2	2 %
2 weeks	7,500 r	34	15	19	44 %	—	—	—
	8,000 r	38	21	17	55 %	—	—	—
A 1 and 2. (delayed treatments)	9,000 r	46	25	21	54 %	3	6	20 %
3 weeks	7,000 r	22	6	16	27 %	—	—	—
	8,000 r	16	6	10	37 %	—	—	—
A. 3	9,000 r	17	8	9	47 %	—	—	—
	10,000 r	36	20	16	56 %	3	0	8 %
4 weeks	7,500 r	19	2	17	11 %	—	—	—
	9,000 r	14	6	8	47 %	—	—	—
B. 1	10,000 r	17	9	8	53 %	—	—	—
	11,000 r	14	7	7	50 %	3	1	28 %
	11,500—12,000 r	36	7	29	20 %	3	10	36 %
5 weeks	8,000 r	37	10	27	27 %	—	—	—
	9,000 r	34	8	26	23 %	0	2	6 %
B. 2 and B. 3	10,000 r	27	10	17	37 %	—	—	—
	10,500 r	64	39	25	60 %	0	2	3 %
	11,500—12,000 r	33	4	29	12 %	3	10	40 %
6 weeks B. 2 and B. 3	10,500—11,000 r	63	48	15	76 %	2	2	6 %
	11,500—12,000 r	76	34	42	45 %	20	15	46 %

Analysis of Results

It has already been pointed out that precalculation of dosage which results in large numbers receiving the same dose in the same period of time makes it necessary to compare the effects produced on groups of cases some large, some small. Each overall time of treatment has been taken separately. The periods of 4, 5 and 6 weeks are taken to the nearest week. The shorter periods do not vary by more than a day. The technique used is indicated by the use of the number given when they were described. The effects of the doses used are shown as the percentage of cases symtom free at the third anniversary of treatment. All cases which were, or subsequently proved to be, diseased were counted as dead leaving only the thirteen indefinite cases shown in the table of cases removed from the sample of 1,601 fully treated cases finally reduced to the 1,523 cases analysed in table 3.

High Dose Effects

The high dose effects recorded are nearly all rectal reactions, late radiation effects on the bladder accounting for a very small proportion of the cases. Rectal reactions were fully described by T. F. TODD (4), who divided them into extrinsic and intrinsic and discussed how they are produced. Immediate reactions are not shown, a transient proctitis or some irritability of the neck of the bladder are common in the first few weeks after treatment and, unless severe and prolonged, do not seem to indicate that the patient will have trouble later. It is probable that all the high dose effects in women symptom-free at the third anniversary have been recorded because notes are made and treatment arranged when they attend for follow-up examination. This is not, however, the case in the patients who have died. It often happens that the first sign that all is not well is failure to keep the usual appointment. The general practitioner then sends in a report of local recurrence often referring to rectal symptoms. Finally, after perhaps another year, a report is received that the patient died with the primary recurrent and metastases in the pelvis. It is not possible to be certain whether or not such a patient had a combination of necrosis and recurrence though the symptoms suggest the possibility. In any case the patient is dead and the treatment has failed.

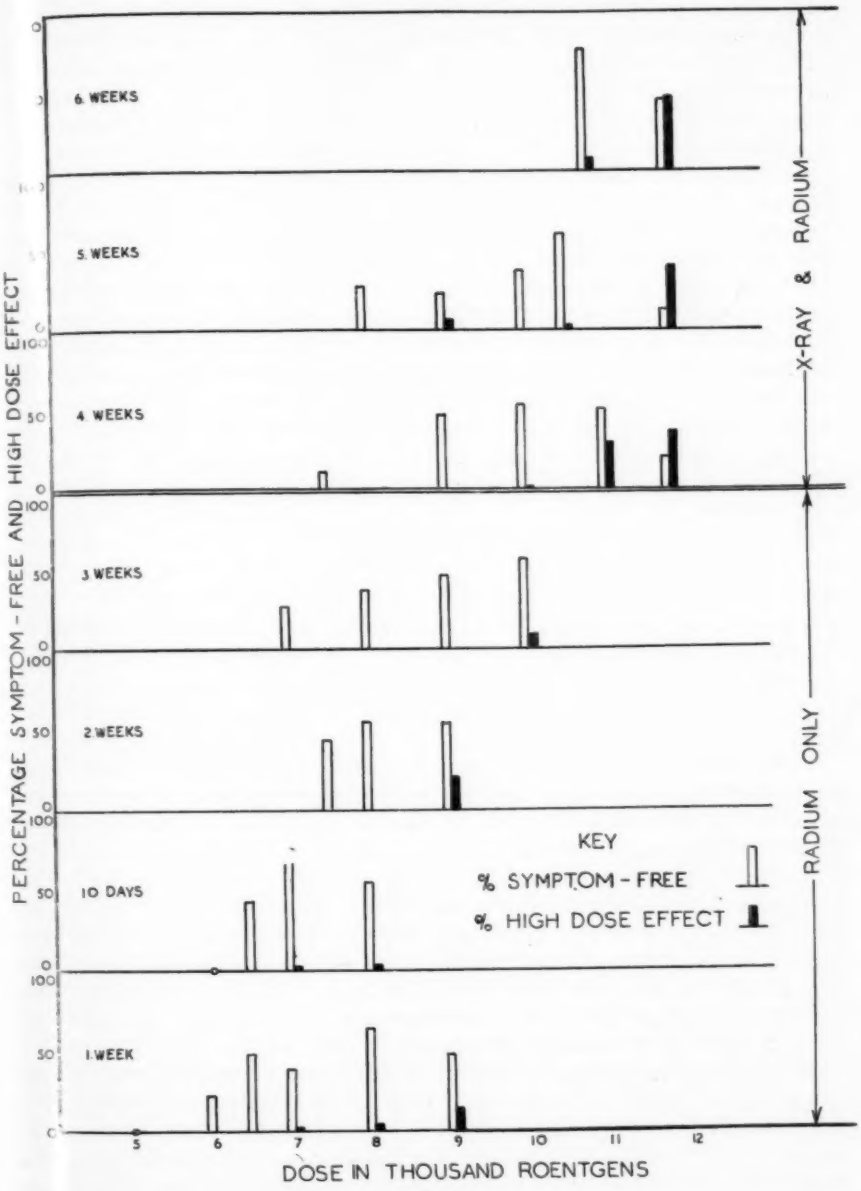
Presentation of Results

From the results shown in Table 3 a modified graph has been prepared which presents the results in a form which the eye can follow and which may be regarded as a series of curves showing the effects of dose at each

of the times chosen. If they are followed in turn the trend is quite clear if two groups, 6,500 r at one week and 7,000 r at ten days which are anomalous for special reasons and have been marked with asterisks, are disregarded. For treatment in one week (A. 1.) the percentage well rises to 64 % at 8,000 r and falls to 47 % at 9,000 r, a difference which is significant for the numbers involved. At ten days (A. 2.) there is a rise to 55 % at 8,000 r and it is possible that the peak has not been reached. At two weeks the numbers are small and the fact that 9,000 r included a small number of patients treated by 4 days roentgen introduces a new factor but there is nothing out of accord with the other findings. At three weeks (A. 3.) the best percentage for radium alone in divided doses is reached at 10,000 r but again it is uncertain, though probable, that this is the peak. The numbers here are small and it should also be recalled that this technique was used in the early years before the dose was preselected. As a result time varied considerably and a few cases probably overlap into other techniques and are seen at 2 weeks and 4 weeks. At 4 weeks the range of combined radium and roentgen treatments is reached and although numbers are not large, the continuous irradiation technique having been abandoned when its effect was realised, the fall from 53 % at 10,000 r to 20 % at 11,500 r to 12,000 r is very striking. At five weeks the same effect is seen, 60 % at 10,000 r with a fall to 12 % at 11,500 r to 12,000 — a contrast which is statistically significant. Finally at six weeks 76 % are symptom-free, a figure which will be referred to again, and at 11,500 to 12,000 r percentage symptom-free falls to 45 %.

Attention should now be given to the percentage of high dose effects shown as dark columns. It is immediately clear that once the peak of optimum dosage has been passed there is a marked increase in the number of high dose effects recorded and the higher the percentage of high dose effects the lower the percentage not only of patients symptom-free but of survival. Before passing to a short discussion of these findings the anomalies in the marked groups must be explained.

The most important is that group which shows results of treatment by 7,000 r in ten days which are better than those by 7,000 r in seven days. The explanation is that after two years of experience with large numbers of cases treated with Radium alone, using a preselected dose of 9,000 r for most of the cases, it was appreciated that the proportion of high dose effects was rather high and that it was greater among the older women, showing that local tolerance is diminished in the atrophic senile uterus of old age. It was, therefore, decided that while dosage in general should be changed to 8,000 r in ten days it should be reduced to 7,000 r in ten days for patients over sixty-five. The good results at this point are, therefore, due in part at least to the better prognosis


6 WEEKS
5 WEEKS
4 WEEKS
3 WEEKS
2 WEEKS
10 DAYS
1 WEEK
X-RAY & RADIUM
RADIUM ONLY
KEY
% SYMPTOM-FREE
% HIGH DOSE EFFECT
PERCENTAGE SYMPTOM-FREE AND HIGH DOSE EFFECT
DOSE IN THOUSAND ROENTGENS
5
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12

of the slow growing cervical cancer of old women, a cancer which may be regarded as analogous to the senile scirrhous cancer of the breast, although the total duration of the disease is less. The same factor may also appear in the group treated with 6,500 r in one week but here the numbers are so small that comparisons are not statistically significant. The same question of lack of significance with small numbers makes it inadvisable to give too much importance to some parts of the graph except in so far as they show a general trend. The actual numbers for any column should, therefore, be referred to before any comparison is made. For example if the figure of 76 % symptom free with 10,500 r in six weeks is tested against the figure of 60 % at five weeks it is barely significant. It was, however, felt that it indicated a trend of sufficient importance to merit further investigation. It was then found that during 1938 and 1939, when the proportion of the dose obtained from roentgen-radiation varied from 30—35 %, there had been a tendency to treat earlier cases with 7,000 r Radium plus 3,000 r Roentgen while more advanced cases had 7,000 r Radium plus 3,500 r or even 4,000 r Roentgen. It is unfortunate that any group may be biased by selection but it is unavoidable in clinical work. To the best of my belief this is the only group which shows any appreciable bias in the stage 1—2—3 ratio and even this is slight as no case in stage 1 had roentgen treatment. It was not found in any of the large groups which all represent fairly evenly stratified samples of patients in all three stages consecutively admitted during the period in which the technique which produced that dose was in use.

Discussion

The salient feature of the graph is a peak of optimum dosage followed where a curve is continued far enough by a sharp drop. There is a suggestion that the curve rises fairly sharply with dose from the region of 6,000 r, flattens out until it reaches the peak and then falls again with a corresponding rise in the percentage of high dose effects. Sub-lethal dosage is a fact which requires no further discussion. A fall in survival rate with an increase in high dose effects when doses exceed tolerance levels should now be accepted as a significant finding of equal importance. The nature of the high dose effect has already been mentioned and in my previous paper I suggested that the term supra-lethal dosage should be used to describe the biological dosage which results in the combination of necrosis and recurrence which all radiotherapists must have seen and not only in cancer of the cervix. Supra-lethal dosage is possible with Radium, as the percentage appearing at 9,000 r radium alone clearly shows, but the effects are more local and even in the cases which died had sometimes been recorded at examination of a patient who became

symptom-free again for a term before recurrence was established. The addition of Roentgen to Radium treatment which must greatly increase the volume of tissue irradiated can easily produce a serious rise in supralethal effects. This is very clearly seen in the bad results of 11,500—12,000 r at four and five weeks and the downward trend with these doses at six weeks. This is not the place to discuss the reasons why the irradiation of large volumes of tissue results not only in a higher proportion of necrosis but also interferes with the resolution of the tumour, but the importance of volume is stressed because optimum dose can only be accepted in relation to the techniques described. A roentgen arrangement which used larger fields or failed to screen the cervix, or a change in the porportion of the dosage delivered by Radium and Roentgen radiation might be disastrous.

Other factors which might influence biological dosage are the dosage rates used and the intervals between treatments. These factors seem to have no importance so far as this series is concerned but the differences were not great. They might have to be considered if other methods were used, for instance the shorter Radium applications and longer intervals of the Stockholm technique.

Conclusions

I believe that this investigation of a further series of 1,513 cases of cancer of the uterine cervix has confirmed some of the tentative suggestions made in the earlier paper. If Radium alone is used, the optimum dose level assessed at point A lies between 7,500 r and 8,000 r in seven days or 8,000 r and 8,500 r in ten days. The best results with Radium alone in this series are with 8,000 r in ten days. An exception is found in the cancer of old women and for patients over 65 the optimum dose appears to be 7,000 r in ten days. For Radium plus small field beam directed roentgen therapy to parametria the optimum dose at four weeks is probably 9,500 r to 10,000 r and at five to six weeks 10,000 r to 10,500 r. The best results in this series were obtained with 10,000 r in six weeks, 7,000 r gamma radiation plus 3,000 r roentgen radiation. The value of a preselected optimum dose is, I believe, brought out in table 1. In 1941 the dose of 8,000 r at A (7,000 for patients over 65 years) in seven days was consistently used and the five year survival rate of 39 % was better than anything previously achieved although there was no change of circumstance or selection of material. During 1942 this preselected dose continued to be used and in 1943 a slight change was made to 8,000 r at A in ten days. The three year survival rates are 1941—45 %, 1942—45 %, 1943—49 % suggesting that the improvement was real and will be maintained. To obtain the optimum dose Radium

alone was used. It is probable that some further advance can be obtained by the judicious addition of roentgen therapy for the more advanced cases and from further narrowing down the assessment of optimum dosage.

SUMMARY

1,601 cases of squamous carcinoma of the uterine cervix in stages 1, 2 and 3 completely treated by radiotherapy are used as material for a study of the effects of dose and time. The techniques used in treatment are described and the use of preselected dosage at a defined point brings together large groups of cases treated with the same dose and in the same time. These groups are analysed and show results as the percentage of treated patients symptom-free on the 3rd anniversary of treatment together with the percentage of high dose effects recorded. These results are shown in the form of graphs and indicate for each of the periods shown 1—6 weeks the dose at which optimum results are obtained. It is concluded that the assessment of optimum doses can be accepted in relation to the techniques described.

ZUSAMMENFASSUNG

1,601 Fälle von Plattenepithelkrebs des Cervix uteri 1., 2. und 3. Stadium, die vollständige Radiotherapie bekommen hatten, werden als Material für eine Untersuchung der Wirkung von Dosis und Zeit verwendet. Die jeweils bei der Behandlung verwendete Technik wird beschrieben, und die Verwendung einer im Voraus gewählten Dosis auf einem bestimmten Zeitpunkt ergibt grosse Gruppen von Fällen, die mit derselben Dosis und in derselben Zeit behandelt wurden. Diese Gruppen werden analysiert und zeigen Ergebnisse, wie den Prozentsatz behandelter Kranken, die 3 Jahre nach der Behandlung symptomfrei waren, sowie den Prozentsatz der angegebenen Folgen grosser Dosen. Diese Resultate werden in graphischer Form vorgelegt und zeigen für jede der Perioden von 1—6 Wochen die Dosis, bei der optimale Resultate erhalten werden. Es wird gefolgert, dass die Berechnung der optimalen Dosis unter Berücksichtigung der hier beschriebenen Technik stattfinden kann.

RÉSUMÉ

1,601 cas de carcinome pavimenteux du col utérin, des stades 1, 2 et 3, qui subirent un traitement radiothérapique complet, servent de matériel pour étudier l'effet des doses et celui du temps. Les techniques employées sont décrites, et la présélection des doses appliquées à tel endroit défini permet de former de grands groupes de cas traités par la même dose et pendant une durée égale.

Ces groupes sont analysés et montrent les résultats obtenus, tel le pourcentage des malades débarrassées de tout symptôme au troisième anniversaire de leur traitement, en même temps que le pourcentage des effets, notés, des doses élevées. Ces résultats sont présentés sous forme de graphiques et indiquent pour chacune des périodes allant de 1 à 6 semaines la dose avec laquelle l'effet optimum est obtenu. La conclusion en est tirée qu'on peut accepter la fixation de doses optimales avec la technique décrite.

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THE TREATMENT OF CARCINOMA OF THE CERVIX COMPLICATED BY PREGNANCY[1]

by

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Carcinoma of the cervix uteri complicated by pregnancy is usually considered as a rare condition. However, while the incidence varies widely in different series, as for instance, at the Mayo Clinic no case in 8,500 obstetric patients, and then two cases seen in 800; and in a series of 3,570 cases of cervical carcinoma 25 were pregnant. The average generally noted is one case in approximately 2,000—3,000 pregnancies. This is frequent enough to require that the obstetrician should carefully examine the cervix in all cases.

In the Woman's Hospital in New York during the past 19 years there were 36,274 obstetric admissions, among which were 10 cases with malignant disease of the cervix, 9 with squamous cell carcinoma and 1 with sarcoma.

The occurrence of carcinoma with pregnancy is usually in pluriparae and in those of advancing age, beyond thirty years. In our series one case was a primipara, and two were twenty-five and twenty-six years of age. Invariably the carcinoma was present before the onset of pregnancy. Authorities differ as to the influence of pregnancy on the growth and malignancy of the cancer. In my opinion, the greatly increased blood supply of the pregnant uterus will naturally tend to increase the rapidity of the growth. The type of cancer cell, the age of the patient, and the stage of pregnancy are factors which determine the result in each individual case and account for why some growths develop more rapidly than others.

The presence of the carcinoma in the cervix tends to cause an abortion, or premature labor, as the growth extends upward. If the growth is confined to the portio of the cervix, the pregnancy may develop normally to term.

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The presence of a growth in the cervix may effect the labor by interfering with normal dilatation, or causing obstruction. Extensive laceration of the cervix may occur with severe hemorrhage. Sepsis is a definite danger.

The passage of the foetus through the diseased cervix crushes the tumor mass and disseminates the cancer cells through the lymphatics and blood vessels.

The diagnosis of carcinoma of the cervix associated with pregnancy may be made more difficult due to the color changes and increased softness of the tissues. The usual symptom is vaginal bleeding or spotting, especially post coital. It is important to differentiate from a threatened abortion, and ectopic pregnancy, or placenta praevia. Any area of induration in the softened cervical tissue or pregnancy should be regarded with suspicion, and wherever an erosion, or suspicious area is present a biopsy taken with the high frequency radio-loop should be done. This technic causes the least trauma and is aseptic. The importance of early diagnosis is obvious. In suspected early pregnancy, if there is any doubt as to the diagnosis, the Aschheim-Zondek test will be of help.

All untreated cases will surely die. The probability of a permanent cure in treated cases is definitely lessened by pregnancy, but the mortality has steadily improved since radio-therapy has been employed. Early recognition of the condition, and prompt treatment by surgery and radio-therapy have improved the cure rate of mother and child.

Depending upon the development of the pregnancy the cases may be divided into two groups — early and late — those before and those after the twenty-eight week or period of viability. In the early pregnancis the foetus will be lost, due to the treatment which is primarily in the interest of the mother. In the late pregnancies beyond the twenty-eight week a Caesarian Section gives the possibility of a favorable prognosis for the child.

In our series of ten cases of carcinoma of the cervix complicated by pregnancy, five were in the non-viable group and five were after the twenty-eight week, or viable. In the five non-viable cases, one was classified as L. of N. I, or early; and in four the carcinoma had extended to the parametrium, L. of N. II. In the five viable cases, two were classified as L. of N. I and three as L. of N. II.

Of the five non-viable cases one only was salvaged for five years, but died subsequently of cancer. She was aged 35 years, three months pregnant with a squamous cell carcinoma L. of N. II. She was given 4,200 mgm. hours of radium, did not abort, and one month after irradiation a supra-cervical hysterectomy and bilateral salpingo-oophorectomy was done. The other four non-viable cases were only irradiated. Two aborted, one in two months, who died ten months later, and one in two

weeks, who died in one year. The other two cases failed to abort — one retained the foetus for thirteen months when a Wertheim operation was done, the patient dying from post operative shock; the other had a missed abortion seven months after the irradiation and died two months later.

In the five viable cases four babies were salvaged and three mothers — one over four years, one seventeen years, and one recent case. Brief histories of these cases are as follows.

1. 77632. Age 41, grav. 5, para 6, 28 weeks pregnant, squamous cell carcinoma of the cervix, L. of N. II. A Porro-Caesarian Section was done with a living child, followed by an application of 3,938 mgm. hours of radium to the vaginal vault and high voltage roentgen therapy. One year later a stricture of the left ureter developed. Sixteen months after the Porro-Caesarian operation a beginning intestinal obstruction occurred. She lived two years and died of recurrence of the carcinoma.

2. 78162. Age 26, para 1. Pregnant full term with a polypoid growth of the cervix which proved to be a sarcoma. An extra-peritoneal Caesarian Section was done with a living child. This was followed by an application to the cervix of 3,000 mgm. hours of radium and roentgen therapy, Coutard technic. Six months later a panhysterectomy and bilateral salpingo-oophorectomy was done as a precautionary measure. Mother and child are alive and well for over four years and nine months.

3. 46898 M. Age 25, grav. 5, para 2, seven and a half months pregnant with a squamous cell carcinoma of the cervix, type II & III, L. of N. II. A Porro-Caesarian Section and bilateral salpingo-oophorectomy was done with a living child weighing 4 lbs. 15 ozs. There was infiltration of the right broad ligament and the right utero-sacral ligament. A high amputation was done with no dissection downward of the bladder peritoneum. Nineteen days post operative 2,984 mgm. hours of radium was applied to the cervical stump, followed by two series of deep roentgen therapy, each of 3,600 roentgens. The mother and child are alive and well nearly seventeen years.

4. 486318. Age 38, para 3, thirty-five weeks pregnant with squamous cell carcinoma of the cervix, type III, L. of N. II. A low flap Caesarian and supra-cervical hysterectomy with bilateral salpingo-oophorectomy was done with a living child. She was referred to us one month later for irradiation therapy. She was given 4,200 mgm. hours of radium to the cervix, followed by Coutard roentgen. She survived one year and two months, dying with a general metastasis.

5. 645000. Age 30, para 5, twenty-nine weeks pregnant with squamous cell carcinoma of the cervix, type II, L. of N. I. A Porro-Caesarian Section was done, the baby died of prematurity. Nineteen days later 3,260 mgm. hours of radium were applied to the cervical stump, followed by Coutard roentgen. The patient has made a good recovery but is too recent to classify.

Treatment

There are differences of opinion as to the best method of treatment of these cases. The first hysterectomy for a carcinoma of a pregnant uterus was done by SPENCER WELLS in 1881.

If the cancer is untreated the pregnancy will go to term in two thirds of the cases, but only one third of the infants will survive delivery by the

vaginal route. All untreated cases will die — therefore prompt treatment of the carcinoma is indicated.

Either the radical Wertheim operation, or irradiation by radium or roentgen may be employed. The consensus of opinion today is in favor of irradiation.

In the non-viable cases, if irradiation alone is used the death of the foetus will result, due to abortion, or if the foetus should continue to develop grave injury to the child may result in malformations or microcephalic idiocy.

In the early pregnancies removal of the uterus by a radical abdominal hysterectomy has been successful in saving six out of nineteen mothers, as reported by PEHAM and AMREICH. This is done without previously evacuating the uterus, and is followed by high voltage roentgen therapy. This method would seem suitable for a very early carcinoma.

Irradiation is the most frequent method and is usually employed in the early non-viable cases without an associated hysterectomy. This will destroy the foetus which may be delivered spontaneously, but not always. Several weeks, or months, after the death of the foetus it may have to be removed by operative procedure. This is objectionable because of the danger of disseminating the cancer.

In all early pregnancies, whether a radical Wertheim operation or irradiation is employed, death of the foetus is inevitable, and the uterus and ovaries are removed, or their function is destroyed. The evacuation of the uterus as a result of irradiation means trauma to the diseased cervix with possible extension of the carcinoma. A supra-cervical hysterectomy in the early months will remove the foetus without disturbing the cervical region and permit the treating of the cervix as a stump carcinoma by irradiation and roentgen. At the same time TAUSSIG's procedure of removing any enlarged glands may be employed.

In cases seen after the twenty-eight week delivery per vaginam is contraindicated on account of the obstruction of a rigid non-dilatable cervix, the result of the disease, and the dissemination of cancer cells which will be caused by the bruising and trauma of a forceps extraction. The classical Porro-Caesarian Section, removing the uterus well above the internal os, without disturbing the bladder, gives the best results for saving the child with the least trauma to the carcinomatous area. In two to three weeks after the operation, irradiation of the cervix stump followed by high voltage roentgen is administered. PORTES and NABIAS were the first to advocate this form of treatment in the viable cases.

I see no reason why such a procedure is not as applicable to the early non-viable cases as to those where there is a viable foetus. A supra-cervical amputation of the uterus is far less dangerous than a radical Wertheim operation, and the results obtained in the treatment of stump

carcinoma by irradiation have been as good and better in our hands, and also in other clinics, as in the ordinary cervix cases.

BEHNEY has reported a ten percent better percentage in his stump cases than in his total series, and SCHEFFEY's salvage was 42.8 % against 20.5 % in his total cases. In our series at the Woman's Hospital we had an absolute survival rate of 42.8 % in stump cases, while our total cases were 28.5 %. As BEHNEY has pointed out, the salvage of stump cases for five years in SCHEFFEY's, BEHNEY's, and our clinic, if combined, was approximately twice that achieved with general carcinoma of the cervix in the same clinics.

The general impression has been that cancer of the stump is more difficult to treat and with less hope of success than cancer of the cervix with the corpus present. I do not believe this is so, and I agree with BEHNEY's statement that stump cancer responds to treatment in a manner similar to cases where no hysterectomy has been done and with generally better results. A retarding factor in the development of the cancer should be expected, due to the diminished circulation and lymphatic drainage caused by the castration combined with the subtotal hysterectomy.

Comment

The type of treatment to be adopted is a perplexing problem, and each case must be individualized, but in view of the results reported by others and our own experience, I believe that in general all early cases of pregnancy where viability of the child is out of the question, a high supracervical hysterectomy and bilateral salpingo-oophorectomy should be first done. This removes the foetus without trauma to the cervix, avoids the abortion or missed abortion with its danger of trauma to the cervix, and sepsis, and disseminating the cancer cells. This should be followed in about two weeks with irradiation of the cervix stump and high voltage roentgen, as in the treatment of all stump carcinoma cases.

In cases in the last three months of pregnancy with a viable child, a Caesarian Section is indicated before irradiation of the cervix. A Porro-Caesarian should be done with removal of the adnexa, and as soon as possible irradiation of the cervix stump, and high voltage roentgen should follow.

The question of irradiating the cervix before the Porro-operation is done may be open to discussion. In general irradiation of a pregnant uterus is inadvisable, due to the damage to the child which may follow, even in late cases, as shown by studies of MURPHY and GOLDSTEIN.

The case reported by Sir COMYNS BERKELEY is one in point. In August, 1914 he operated before a group of us, who were visiting in London, on a case at term with a carcinoma of the cervix (evidently an early

ne). She had been irradiated previously at the twenty-sixth week when irst seen. He did a classical caesarian with a living child and at the same itting did a radical Wertheim operation. The child had two bald patches n an otherwise hairy head, these being surely due to the action of the adium. He reported the patient as alive and well, and the child also, wenty years later in 1934.

In a patient who is in the sixth month of her pregnancy and who is anxious for a child, a minimum dosage of irradiation of the cervix may be given first. This will temporarily arrest the progress of the carcinoma. When viability is attained the Porro-Operation is done, followed by deep roentgen therapy.

SUMMARY

As a result of the reports of others and in the light of own experience, the author has come to the following conclusions. An adequate speculum examination of the cervix and vagina should be made in every case of pregnancy, and a biopsy taken in every suspicious case. Irradiation of the cervix by radium and high voltage roentgen associated with supracervical hysterectomy and bilateral salpingo-oophorectomy is the most desirable treatment for the carcinoma of the cervix complicated by pregnancy. In the nonviable cases, a supracervical hysterectomy should be done immediately, sacrificing the foetus, and as soon as recovery warrants, irradiation of the cervix stump followed by high voltage roentgen therapy, thus avoiding the trauma to the cervix in evacuating the uterus, and the danger of disseminating the cancer cells, also obtaining the benefit of the retarding factor resulting from the castration. In pregnancy seen at the sixth month, where a child is anxiously desired, irradiation of the cervix may be done before the hysterectomy in the hope of getting a living child. In all viable cases a Porro-Caesarian Section should be first done, followed by irradiation of the cervix stump and high voltage roentgen therapy.

ZUSAMMENFASSUNG

An Hand der Mitteilungen anderer und angesichts seiner eigenen Erfahrungen ist Verf. zu folgenden Schlussfolgerungen gekommen. Eine sachgemässe Spekulumuntersuchung des Zervix und der Scheide sollte bei jedem Falle von Schwangerschaft vorgenommen werden, und in jedem verdächtigen Falle sollte Probeexzision gemacht werden. Bestrahlung des Zervix mit Radium und hochgespannten Röntgenstrahlen, kombiniert mit suprazervikaler Hysterektomie und beiderseitiger Salpingo-oophorektomie, stellt bei dem durch Schwangerschaft komplizierten Zervixkrebs die Behandlung der Wahl dar. Bei noch nicht lebensfähigem Fötus muss sofort eine suprazervikale Hysterektomie vorgenommen und der Fötus geopfert werden, und so bald die Kranke sich erholt, der Zervixstumpf bestrahlt werden mit nachfolgender Hochvolt-Röntgentherapie, wodurch das bei der Entleerung der Gebärmutter entstehende Zervixtrauma und die Gefahr der Verschleppung von Krebszellen vermieden wird, und man ausserdem den Vorzug der hemmenden Wirkung der Kastration erhält. Bei Schwangerschaft im sechsten Monat kann man, wenn die Kranke intensiv ein Kind wünscht, vor der Hysterektomie (in der Hoffnung, ein lebendiges Kind zu erhalten) eineBestrahlung des Zervix vornehmen. Bei allen lebensfähigen Fällen muss zuerst ein Porro-Kaiserschnitt vorgenommen werden und darauf Bestrahlung der Zervixstumpfes und Hochvolt-Röntgenbehandlung gegeben werden.

RÉSUMÉ

En se basant sur les exposés d'autres sources, et à la lumière de ses propres expériences, l'auteur est arrivé aux conclusions suivantes. Un examen adéquat, au spéculum, du col et du vagin devrait être fait dans tous les cas de grossesse, et une biopsie pratiquée chaque fois qu'il y a le moindre soupçon. L'irradiation du col par le radium et les Rayons Roentgen de haut voltage, associée à l'hystérectomie supravaginale avec ablation bilatérale des annexes est le traitement le plus désirable du carcinome du col compliqué de grossesse. Quand le foetus n'est pas viable il faut le sacrifier en faisant immédiatement une hystérectomie subtotale; et aussitôt que la convalescence le permet, on procédera à l'irradiation du moignon cervical, suivie de roentgenthérapie de haut voltage, évitant ainsi le traumatisme du col lors de l'évacuation de l'utérus et le danger de dissémination des cellules cancéreuses, tout en obtenant aussi le bénéfice de l'action retardante due à la castration. Dans les cas de grossesse vus au sixième mois, là où le désir d'un enfant est très grand, on peut irradier le col avant l'hystérectomie, dans l'espoir d'avoir une progéniture vivante. Dans tous les cas où l'enfant vit, il conviendrait de faire d'abord un Porro, suivi d'irradiation du moignon cervical et de roentgenthérapie de haut voltage.

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FROM THE PRESBYTERIAN HOSPITAL, NEW YORK CITY

TISSUE DOSAGE IN ROENTGENTHERAPY OF MAMMARY CANCER[1]

by

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Roentgentherapy of cancer of the breast has been in use since GOCHT (6) first applied it, in two non-operated cases in 1897. There is, however, still no agreement as to its exact value, either when used as the only treatment or when combined with mastectomy as pre- or postoperative therapy. It is generally admitted that the results of roentgentherapy vary chiefly with the extent of the cancer prior to irradiation and with the dosage delivered to the tumor. Yet attempts are often made to evaluate this treatment without considering these factors, especially that of tissue dosage. A hidden factor which influences the tumor dose is that of personal care and accurate installation of the case. No one would think of comparing the work of an old, experienced surgeon with that of a young intern doing his first radical mastectomy; yet the results of roentgentherapy are evaluated irrespective of whether the treatment is given by a qualified radiotherapist, a novice or at times even a technician.

Postoperative Roentgentherapy

Classification of the case to be irradiated, as Steinthal I, II or III permits of only gross grouping as it is the more advanced cases in each clinical group which chiefly are chosen for postoperative roentgentherapy. If a surgeon were certain that he had completely removed the cancer, he would not be likely to recommend postoperative roentgentherapy. Even the crude separation into Steinthal's or similar anatomic groups, however, is of help in postoperative roentgentherapy. The more extensive the cancer before mastectomy the greater the likelihood that at the time of treatment there will be unrecognized local recurrences. The presence of these persisting cancer foci influences the results of radiotherapy as much as the skill of the operator, or the amount of

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subcutaneous tissue removed at the time of operation. Postoperative roentgentherapy is given in the hope of arresting these microscopic, clinically not recognizable cancer foci in the mastectomy area, axillary tissues, supraclavicular and infraclavicular lymph nodes or in those of the anterior mediastinal or internal mammary chain. Unfortunately, body tolerance is inadequate to permit the application of cancericidal dosage to distant metastases, though it is these and not the local disease which are responsible for the death of most patients. Progressive growth of distant metastases, if present when radiotherapy is begun, is not influenced by any local improvement in the irradiated areas. The fields which are irradiated and the dosage given have varied in different clinics and in different periods of the history of radiotherapy. Routine irradiation of the operated chest wall, axilla, supra- and infraclavicular region on the same side is done in most clinics. At the Presbyterian Hospital where meticulous and very radical mastectomy is customary, recurrences in the axilla are uncommon and we are not in the habit of irradiating this region. Where less radical surgery is done the axilla should probably be treated. Most lymph node metastases in the supraclavicular region occur above the inner third of the clavicle, and it is this part of the supraclavicular area on which attention should be concentrated. The greater likelihood of extension to the anterior mediastinal and internal mammary chain of lymph nodes from inner quadrant tumors increases justification for postoperative roentgentherapy in cancers of this location. Subcutaneous nodules in the intercostal spaces, along the sternum, may represent extensions from lymph node metastases in the internal mammary chain, thus they require a different type of irradiation than if the disease were limited to the skin.

While there is no proof that it takes less tumor dosage to destroy a microscopic focus of cancer than one which is large enough to be clinically recognizable, the experience of McWHIRTER (16) suggests that important growth restraint for at least three years may be obtained by a tissue dose of 3,500 to 4,500 r given in four weeks. This, he administers after radical mastectomy to the »supraclavicular region, the whole length of the axillary chain of glands and the chest wall on the affected side». Comparing surgery alone with surgery plus radiotherapy, the reduction in his total recurrence rate in the treated area three years postoperatively, is impressive. Classifying his 1,255 cases into three clinical stages according to RALSTON PATERSON, the difference in favor of surgery with postoperative radiotherapy was 18 % in Stage I breast cancer, 18.8 % for Stage II and 20.2 % for Stage III. He also had 400 stage IV cases, but naturally did not use these hopelessly advanced cases for purposes of comparison.

Dosages employed by the older authors (10), (17) and those currently

used in the United States are very much weaker. Thus, WESTERMARK (1) gave three to four series of treatments in one and a half years, each series consisting of four to six treatments of 1/4 to 1/6 erythema dose. The tissue doses in most of the clinics in the United States vary from a few hundred to at most 2,500 r and the time period from a few weeks to one and a half years. PORTMANN (18), for instance, administers 800 r, repeated in four months and again in eight months.

At the Presbyterian Hospital, New York, routine postoperative prophylactic roentgentherapy has been given up, though at times postoperative irradiation is used when requested. Between 1923 and 1929, it was customary to administer tumor doses from 300 to 2,300 r within six months after mastectomy. The survival of 78 patients thus treated did not appear to be influenced by this treatment and 8 of 9 cases of skin metastases started in the irradiated operative area of the anterior chest wall (13).

Tangential irradiation (5) of the anterior mediastinal or internal mammary lymph nodes, with beams skimming along the chest wall so as to avoid the lungs occasionally may miss the nodes. Direct anteroposterior irradiation is simpler, yet intensive irradiation of these nodes also irradiates the lungs; this may produce a radiation pneumonitis, especially if the daily or total dosage is great and the irradiated fields are large. So as to reduce this danger 130 Kv. 3 mm Al 50 cm T. S. D. is preferred by some, while others employ 200 Kv. 0.5 mm Cu 50 cm T. S. D. The dosage reaching the anterior mediastinal lymph nodes by these two technics may differ. For instance, a piece of sternum 8 mm thick will absorb 17 % of the irradiation given by the 130 Kv. technic and only 5 % of the 200 Kv. roentgen therapy.

Varying extents of involvement, treated with different tumor dosages and technics are all comprised under the heading of postoperative roentgen therapy and as such, the results are extolled by its supporters and decried by its opponents. While no one would think of compiling jointly the results of radical mastectomy and excision limited to the primary tumor, there are constant comparisons made between non-irradiated series of cases and those receiving postoperative roentgentherapy, irrespective of whether the tumor dosage is a few hundred or several thousand roentgens.

Preoperative Roentgentherapy

The differences in cancericidal effects of varying tumor dosages may be readily seen, if one studies the microscopic changes in preoperatively irradiated mastectomy specimens. Direct radiation injury to cancer cells may be appreciated quickly, that which occurs through damage to blood

vessels and connective tissue takes longer to appear. For a complete radiation effect, therefore, a sufficient interval must elapse between radiotherapy and mastectomy. In 1932, LEE, PACK, QUIMBY and STEWART (11) stated that »the pathologic changes produced in mammary cancer by external irradiation are mainly due to vascular effects» and believed that »an efficient devitalizing dose cannot be delivered by external irradiation alone». They postulate that »the universal tissue dosage necessary to effect destruction of a radio-resistant mammary cancer approximates twelve skin erythema doses». Four years later, however, ADAIR (1) also reporting from the Memorial Hospital, claimed that in 33 % of 18 cases of breast cancer, complete microscopic disappearance of the breast cancer was obtained by external roentgen therapy. In ADAIR's cases 1,800 r was administered through each a mesial and lateral breast field with 200 Kv. roentgen therapy; whereas, most of the cases reported by LEE, et al. had been treated with lesser dosage and lower voltages. In 1939, BACLESSE, GRICOUROFF and TAILHEFER (2) reported on a study of 21 preoperatively irradiated cancers of the breast. In spite of »very large» dosage they felt certain of only two cases in which they thought they had demonstrated a complete disappearance of cancer from the breast, while cancer persisted in the axillary lymph nodes. In 1940, HALLEY and MELNICK (8) studied 21 cases in which tumor doses of 1,200 to 4,500 r were administered in eleven to forty-nine days; the intervals between the radiotherapy and mastectomy varying from one to forty-five days. They saw regrowth of surviving tumor cells in four to six weeks after termination of therapy, and, therefore, advised mastectomy within the first two or three weeks after radiation. In 1942, HARRIS (9) found that only 13 % of 75 patients showed sterilization of the primary tumor in the breast when exposed preoperatively to tumor doses up to 4,500 or 5,000 r. In 1943, DANN and KORITSCHONER (4) reported 10 preoperatively treated cases with tumor doses up to 4,500 r and concluded that »complete sterilization of carcinoma of the breast and axillary nodes by fractionated irradiation has not been accomplished». HOFFMEYER (Acta radiol. 24: 421—429, 1943) arrived at similar conclusions on a basis of 53 pre-operatively irradiated cases but using smaller doses.

Between 1933 and 1937, 38 patients were given preoperative roentgentherapy at the Presbyterian Hospital, New York (13). The breast and axilla received up to, but not exceeding 4,500 r tumor dose, in six to eight weeks and mastectomy was done from a few days to over one year later. At most 2,000 r/o were administered to each superior, inferior, mesial and lateral breast field. The roentgen beams were placed tangentially skimming along the chest wall in an effort to exclude the deeper portions of the lungs. The fields varied according to the extent and position

of the tumor and the size of the breast. As much of the breast as possible was irradiated; fields varying from 8 × 10 cm to 10 × 15 cm; the latter size was used more commonly when only two opposing fields were irradiated. A voltage of 200 Kv. 0.5 to 2 mm Cu or Thoraeus filter and a 50 cm T. S. D. were employed. The axilla was attacked in a similar way, through an 8 × 10 cm or slightly larger anterior, posterior and direct axillary field. The tumor doses varied up to 4,500 r and the air doses up to 2,000 r to each of these three areas. Grossly, the tumours often disappeared. In nine cases specimens obtained at biopsy and at mastectomy were available for comparison of their microscopic appearance. There were noted vacuolization, pyknosis, swelling of the cells and nuclei, atypical mitoses, reduction in the number of mitoses and sclerosis of the stroma. Nevertheless, cancer cells could be demonstrated by Dr. STOUT and his co-workers in every specimen. In one, in which the interval between the last treatment and the mastectomy was over a year and the tumor dose 4,500 r, necrosis of the cancer cells and other radiation changes were especially marked. According to ASA BEACH (3), who also reported this case, the stroma consisted of masses of dense collagen much of which was markedly degenerated and almost acellular. The few large vessels present »showed marked degeneration of the elastic lamina and intimal thickening. Many small veins contained organized thrombi». In spite of this tremendous radiation damage, 20 cancer cells were demonstrated after a very thorough and careful search. One might speculate as to whether the 20 poorly stained cancer cells were viable or whether they would have died and been absorbed had a mastectomy not been done. In view of their presence, however, complete destruction of the cancer could not be claimed. It thus became evident to us, just as it had to the authors mentioned above, that a preoperatively administered tumor dosage of 4,500 r was inadequate to permanently arrest cancer of the breast. As result of this investigation the question naturally arose as to whether still higher tumor dosage would sterilize breast cancer and eventually permit to do away with the need for radical mastectomy.

In 1938, HAAGENSEN and STOUT (7) reviewed the results in 640 radical mastectomies performed at the Presbyterian Hospital, New York, between 1915 and 1934. They postulated certain criteria of inoperability and separated 109 of the 640 operated patients which in retrospect they now classified as inoperable. They then found that all of these 109 patients died within five years after radical mastectomy. Next they compared the survival of these cases with 343 untreated cases published by DALAND and LAZARUS-BARLOW, and came to the conclusion that »radical mastectomy in cases in which the disease is locally so far advanced that cure cannot be obtained, shortens the patient's expectation

of life by about ten months». The criteria of inoperability they postulated were as follows:

Women of all age-groups, who are in good enough general condition to run the risk of major surgery, should be treated by radical mastectomy, except as follows:

1. When the carcinoma is one which developed during pregnancy or lactation.
2. When extensive edema of the skin over the breast is present.
3. When satellite nodules are present in the skin over the breast.
4. When intercostal or parasternal tumor nodules are present.
5. When there is edema of the arm.
6. When proved supraclavicular metastases are present.
7. When the carcinoma is the inflammatory type.
8. When distant metastases are demonstrated.
9. When any two, or more, of the following signs of locally advanced carcinoma are present.

a) Ulceration of the skin.

b) Edema of the skin of limited extent (less than one-third of the skin over the breast involved).

c) Fixation of the tumor to the chest wall.

d) Axillary lymph nodes measuring 2.5 cm or more, in transverse diameter, and proved to contain metastases by biopsy.

e) Fixation of axillary lymph nodes to the skin or the deep structures of the axilla, and proved to contain metastases on biopsy.

In view of this study it was concluded in the Neoplasm Clinic of the Presbyterian Hospital not to do radical mastectomy on cases conforming to the above criteria but to refer them for roentgentherapy.

Roentgentherapy of Inoperable Mammary Cancer

During 1938, 1939 and 1940, 46 patients with non-operated cancer of the breast were thus referred for roentgentherapy. These were reviewed in 1946 (15) and again in April, May and June, 1947. Supraclavicular and distant metastases on admission or soon thereafter were present in many. In retrospect, it seems futile to have attempted to influence such widely spread cancers by local roentgentherapy to the breast tumor and axillary metastases. In a number, however, it was not realized that distant metastases were already present, as clinical and radiographic evidence of such spread was still lacking. Gross regression of the tumor in the breast and axillary lymph nodes in these cases did not influence the clinical course of the disease any more than had these patients been treated by radical mastectomy.

Fifteen patients were given tumor doses of less than 5,500 r. The primary tumor though smaller persisted in all. Thirty-two of the patients were given tumor doses of 5,500 to 8,000 r to the breast. In addition to the 2,000 r/o to each of the four breast fields described in the preoperatively treated series there were added another 1,000 to 2,500 r directly to the tumor, and in addition in some 2,500 r/o was given to each of the four breast fields instead of 2,000 r/o. The axilla was crossfired through each, an anterior, posterior and direct axillary field with doses varying between 2,500 to 3,000 r/o. The daily doses varied from 100 to 200 r/o each to two opposing, either breast or axillary fields, so that it took between two and one half and three months to administer the treatment. The same technical factors were used as in the preoperative series except that 130 Kv. 3 mm Al and 50 cm T. S. D. was often substituted for the 200 Kv. technic for the field directly over the primary breast tumor. At times we had to stop for a week or longer to allow subsidence of a severe skin reaction. The irradiated skin usually shed completely leaving a denuded slowly healing area. The nipple area was most painful and healed slowest while the infra-mammary and axillary folds showed tendency to maceration causing considerable discomfort. A number of the cases later developed telangiectasia, atrophy of the irradiated area and at times, a typical indurated thickened radiation sclerosis especially when the treatment was given more rapidly or with higher doses.

Of the 32 patients receiving a tumor dose of between 5,500 to 8,000 r the tumor disappeared grossly in 24 and persisted in 8. Twenty-one of the 32 are dead, one of these not showing any clinical evidence of activity for six years, one is now dying from cancer, one died of a coronary occlusion over five years after this treatment and nine are now alive and free from clinical evidence of cancer from seven to nine years after their radiotherapy treatment. None of these ten »arrested» cases had supraclavicular, skin or distant metastases. No claim is made that these ten cases are cured. It may readily be that in all of them cancer cells are quietly reposing amidst sclerotic stroma awaiting an opportunity to again start growing. Our fear as to our inability to completely destroy the cancer with our present technic is supported by the post-mortem finding of well stained cancer cells in the breast of a patient dying of general metastases from cancer of the left breast, seven months after a tumor dose of 6,930 r to the breast. Two of the cases which remained well for several years, later developed renewed activity in the irradiated area and distant metastases. All of these cases, however, were far advanced fulfilling HAAGENSEN and STOUT's prerequisites for classification as inoperable. Thus, had a radical mastectomy been done on them they would probably have died within five years.

Of those patients who died, en cuirasse involvement was present

in four of eight, in which the tumor persisted grossly. Three deaths were due to pulmonary, six to skeletal metastases and in one the cause of death was undetermined. Four died from cardiovascular disease without clinical evidence of cancer but less than five years after treatment.

It seems justifiable to limit the large doses described in the foregoing paragraphs to those patients in whom the disease though inoperable is confined to the breast and axilla, since it was only in these cases that we succeeded in arresting the cancer.

The importance of tumor dosage in patients with distant metastases is much less, the unrecognized and non-irradiated metastases progress in accordance with the natural clinical course of the cancer irrespective of regression of those which have been irradiated. The time during which the growth of a particular metastasis will remain restrained, however, is influenced by the tumor dose delivered to that metastasis, especially if the natural clinical course of the disease is slow.

Natural Clinical Course

The natural clinical history of breast cancer varies. Everyone with experience in cancer of the breast has seen patients in whom the entire course of the disease from the appearance of the lump in the breast to death was less than a year, in spite of radical mastectomy and postoperative roentgentherapy. There are other patients, however, who in spite of no treatment advance slowly. A patient avoided all doctors for twenty-two years after she had been advised to have a radical mastectomy. By the time she appeared at the Bassett Hospital in Cooperstown, the breast and adjacent chest wall had been eroded by the cancer and she came in chiefly for roentgentherapy of painful skeletal metastases. Since she had had no treatment and was still alive at the end of twenty-two years, only the slow natural course of her disease was responsible for her survival.

The slower, more cohesive growth of well differentiated, as contrasted with the more diffuse and rapid spread of poorly differentiated cancers of the breast probably accounts for the fact that in the former the results of mastectomy are better (7) than in the latter and that this tendency to slower growth continues even after the appearance of skeletal metastases (12).

In conclusion it may be stated that:

1) The tumor dose has a deciding influence on the result of roentgen therapy of cancer of the breast, providing that the entire diseased area is included in the field of irradiation.

2) A tumor dose of 4,500 r while not destroying cancer completely, probably has a strong restraining influence upon it. Lesser doses have lesser effect.

3) A tumor dose of 6,000 to 8,000 r causes greater growth restraint and perhaps destruction of some of the more radiosensitive cancers. In 10 of 32 patients thus treated the growth of the cancer has been restrained so that there has not been any clinical evidence of cancer for from seven to nine years, since the last treatment. It is not claimed that these cases are cured as microscopic evidence of persisting cancer was found in a breast irradiated even with this dose.

4) In view of these findings radical mastectomy is to be preferred in all operable cancers of the breast. Strict separation of cases according to HAAGENSEN and STOUT, or similar, criteria into operable and inoperable cases is, however, of the utmost importance and in the latter group no surgery, but only roentgen therapy should be attempted.

5) Such separation will reduce the need for postoperative roentgentherapy to cases in which due to a mistaken clinical estimate of the extent of the disease, the surgeon has operated on an inoperable case. Postoperative roentgentherapy becomes more important the greater the preoperative extent of the cancer and the less radical the mastectomy.

SUMMARY

A review of 162 patients receiving roentgentherapy for cancer of the breast as pre- or post-operative, or as sole treatment, at the Presbyterian Hospital, New York, between 1923—1940 shows that tissue dosage influences the therapeutic result. A tumor dose of less than 2,000 r results in little growth restraint; viable cancer cells in mastectomy specimen are found even after a tumor dose of 4,500 r given preoperatively. Ten non-operated cancers clinically limited to the breast and axilla are free from clinical evidence of cancer for seven to ten years after tumor doses of 6,000—8,000 r.

ZUSAMMENFASSUNG

Eine Durchsicht von 162 Kranken, die in den Jahren 1923—1940 im Presbyterianischen Krankenhause in New York wegen Brustkrebs Röntgenbehandlung erhalten hatten (in Form prä- oder postoperativer Bestrahlung oder als einzige Behandlung), zeigt, dass die Gewebedosierung die Behandlungsergebnisse beeinflusst. Eine Tumordosis von weniger als 2,000 r gibt nur geringe Wachstumshemmung; lebensfähige Krebszellen werden noch nach einer präoperativ gegebenen Tumordosis von 4,500 r in Mastektomiepräparaten gefunden. Zehn nicht-operierte Krebse, die klinisch auf die Brust und die Achselhöhle begrenzt waren, wurden sieben bis zehn Jahre nach Tumordosen von 6,000—8,000 r frei von klinischen Anzeichen von Krebs gefunden.

RÉSUMÉ

La revue de 162 malades, soumises à l'Hôpital Presbytérien de New-York, entre 1923 et 1940, à la radiothérapie pour cancer du sein soit comme traitement pré- ou postopératoire, soit comme seule mesure thérapeutique, montre que la dose reçue par les tissus influence le résultat thérapeutique. Une dose tumorale de moins de 2,000 r n'entraîne qu'un faible ralentissement de la croissance; des cellules cancéreuses viables sont

trouvées dans les pièces de mastectomie même après une dose tumorale de 4,500 r d-ministrée avant l'opération. Dix cas, non opérés, de cancer limité cliniquement au s in et à l'aisselle sont indemnes de toute manifestation clinique de néoplasie au bout de à 10 ans, après avoir reçu des doses tumorales de 6,000—8,000 r.

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LE TRAITEMENT DU CANCER DU SEIN PAR CURIETHERAPIE ET ROENTGENTHERAPIE[1]

par

J. Maisin

Le cancer du sein est un des cancers humains des plus fréquents et des plus graves. Son étiologie a été bien étudiée chez l'animal, chez la souris en particulier. L'état actuel des recherches chez la souris permet d'affirmer d'une façon un peu lapidaire que 30 % des facteurs étiologiques relèvent de l'hérédité, 30 % de troubles endocriniens et 30 % de l'influence du facteur lacté. L'existence du facteur «lait» n'a pas été démontrée chez l'homme, par contre l'influence de troubles endocrinologiques paraît reconnue et acceptée par la plupart des auteurs. La part qui revient à l'hérédité chez l'homme n'est pas connue et c'est là un domaine toujours fortement discuté. Le domaine de la thérapeutique du cancer du sein est un de ceux où la thérapeutique radiologique s'est le plus timidement aventurée. Nous croyons que cette hésitation provient d'une part du fait que les classiques en radiologie ont cru à sa radiorésistance et d'autre part, du fait que le sein est un organe facilement enlevable quasi sans danger par le chirurgien au cours d'une opération large réséquant en bloc le cancer et les voies lymphatiques les plus proches. Nous pensons que l'on s'est trop laissé impressionner par l'élégance, la facilité et les bons résultats immédiats de l'opération de Halsted et qu'on n'a pas eu l'attention suffisamment attirée par les résultats éloignés. Le cancer du sein de la femme est au point de vue récidives un des cancers les plus décevants. Tout praticien qui a une certaine expérience dans la matière sait que pour ce cancer la période d'observation de cinq ans après l'acte chirurgical n'a pas grande signification. Les récidives après 10, 15 ans et plus ne sont pas rares. Nous en avons soigné de nombreuses après plus de 20 ans et le professeur Hartmann de Paris en a signalé un cas extraordinaire après un demi siècle. En fait pour le cancer du sein, plus que pour n'importe quel

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autre cancer humain on n'est jamais assuré d'une véritable guérison. Par contre, l'observation clinique de récidives après ce très grand nombre d'années de guérison apparente, sans aucun signe de maladie, nous apporte la preuve non seulement que l'organisme humain peut, par ses propres moyens, lutter longtemps et très efficacement contre des métastases latentes, mais aussi que la destruction de la dernière cellule cancéreuse n'est nullement indispensable et que l'état de santé «clinique» est parfaitement compatible avec la persistence de cellules néoplasiques quiescentes. Ces remarques ont leur importance pensons-nous pour guider la conduite des thérapeutes et nous croyons que ces faits n'ont pas été suffisamment médités par les cliniciens. Ceux-ci dans leur désir très justifié de rechercher la thérapeutique d'efficacité absolue, ont trop négligé certaines autres thérapeutiques qui tout en ne répondant pas à ce critère sont néanmoins, pour le malade, des armes de très grande valeur et souvent les plus efficaces dans la pratique.

Cancers du sein opérables

Nous avons en 15 ans soigné 290 cas appartenant à cette catégorie. Tous ont été soignés exclusivement par radiations. Nous rangeons dans cette catégorie les cas du type I et du type II de Steinthal c-à-d. les cas sans métastases décelables et les cas présentant des métastases uniquement dans le creux axillaire. Il est impossible, sans opération suivie d'examen microscopique des ganglions axillaires, de faire à coup sûr la disctinction entre les cas appartenant à l'une ou l'autre de ces catégories.

Le diagnostic est posé par biopsie. Quand il s'agit de cas présentant une tumeur assez considérable, la biopsie est faite par l'aiguille à ponction qui, dans ce genre de cas, permet presque à coup sûr de prélever aisément un fragment permettant de faire le diagnostic. Dans les cas de petite tumeur, l'acte biopsique consiste dans l'enlèvement total de la tumeur au bistouri électrique, enlèvement précédé d'irradiation externe de la tumeur par une dose de 500 à 750 r mesurés dans l'air.

Voici comment nous avons l'habitude de conduire le traitement. Nous commençons par irradier directement le sein par voie externe par téléradium ou par rayons roentgen. Le champ couvre largement l'entièreté du sein. Après une dose de 750 r nous procédons à l'enlèvement biopsique au bistouri électrique de l'entièreté de la petite tumeur. En cas de tumeur plus considérable nous faisons une biopsie par ponction au trocard coupant. En attendant la réponse de l'examen microscopique nous continuons à irradier la malade au niveau du creux axillaire où nous délivrons une dose de même ordre de grandeur. Si la tumeur est localisée dans la partie supérieure du sein, le creux sus-claviculaire est irradié de même façon.

Si le résultat de la biopsie est positif, nous passons alors à la curiepuncture. Il est évident que si le résultat de la biopsie est absolument négatif nous cessons toute irradiation au reçu de celui-ci.

Le temps curiethérapie est certes, dans notre technique, le temps le plus important. Comme la biopsie, cette curiepuncture est faite sans danger d'essaimage ou avec le strict minimum de danger d'essaimage puisqu'elle a été précédée d'une irradiation de tout le territoire à aiguiller. Ce territoire correspond d'une façon très générale à celui qu'enleverait le chirurgien au cours d'une opération de Halsted bien faite. Nous avons coutume d'appeler cet acte de curiepuncture, un Curie-Halsted ou un radium-Halsted. Il intéresse donc l'entièreté de la glande mammaire et le creux axillaire. Tout ce vaste territoire est uniformément aiguillé. La densité d'aiguillage est toutefois nettement plus prononcée au niveau de la tumeur ou de son ancien nid ainsi qu'au niveau des ganglions cliniquement métastatiques. A ces niveaux il faut tendre à placer les aiguilles les unes des autres à une distance qui n'excède pas $1^1/_2$ cm, rarement on tolérera une distance de 2 centimètres. Il faut les placer en autant de plans que nécessaires pour couvrir l'entièreté de la tumeur. En dehors des régions cliniquement envahies, les aiguilles peuvent être disposées sur des rangées distantes de 2 à 3 centimètres l'une de l'autre. Pour effectuer correctement un tel aiguillage, il faut donc disposer d'un matériel curiethérapique important, d'autant plus important que la tumeur et les seins de la malade sont plus volumineux. De plus les aiguilles doivent être de longueur appropriée. Les aiguilles sont suturées à la peau. Notre matériel ordinaire est constitué par des aiguilles filtrées par $^1/_2$ millimètre de platine. Leur charge est de 1 milligramme par 1.5 centimètre de longueur radiante. Nous disposons d'aiguilles qui ont un foyer radiant de 3 centimètres ou de 4.5 centimètres, longueurs auxquelles il faut ajouter celles de la pointe et du chât. Avec un tel matériel on peut se permettre d'aiguiller les seins même très volumineux. La dose totale utilisée varie évidemment d'après les volumes à irradier. Il nous arrive de devoir employer des doses totales de 100 à 120 milligrammes. La durée de l'irradiation est en moyenne de 5 jours pleins. Il nous arrive toutefois de laisser les aiguilles en place pendant 7 jours. Cette durée d'implantation est fonction de divers facteurs parmi lesquels entrent en ligne de compte la dose totale utilisée, la masse de tumeur à irradier, la distance entre les aiguilles et la dose complémentaire de rayons roentgen ou de téléradium que l'on décide de donner.

L'intervention est très généralement faite sous anesthésie locale ou sous anesthésie au protoxyde d'azote. La quantité de novocaïne à utiliser est toujours importante, jamais toutefois, nous n'avons vu survenir d'incident grave suite à l'emploi de telles doses. Au réveil il est rarement nécessaire de donner un analgésique. Les suites immédiates d'un tel

aiguillage sont banales. A part un peu de dépression ou d'inappétence il n'y a aucune suite désagréable pendant le port des aiguilles. Après leur enlèvement les petits ennuis rétrocèdent rapidement. Il est évident que toute l'intervention doit être faite avec une asepsie rigoureuse, comme celle requise pour toute intervention chirurgicale.

L'aiguillage terminé, nous continuons généralement l'irradiation externe commencée avant l'aiguillage. Quand il s'agit des rayons roentgen nous allons jusqu'à donner au niveau du sein une dose totale de 1,000 à 1,500 r, mesurés dans l'air, et au niveau du creux axillaire une dose de même ordre de grandeur. Si nous estimons de par l'emplacement et l'extension des lésions, que le creux sus-claviculaire doive être irradié nous donnons généralement un minimum de 1,500 r au niveau de cette région qui n'est pas aiguillée. Si nous utilisons le téléradium comme agent d'irradiation externe le nombre de r administré est évidemment plus considérable. La charge de notre appareil a varié de 6 à 11 grammes au cours des années sur lesquelles s'étale l'observation des cas qui font le sujet de cette publication. La distance à laquelle nous avons travaillé a été de 12 à 15 centimètres. Les doses totales ainsi administrées ont été en moyenne de 2,500 r au niveau du sein, de 2,500 r au niveau du creux axillaire, et de 3,000 à 4,000 r au niveau du creux sus-claviculaire. Toutes ces mesures sont faites dans l'air.

L'entièreté du traitement, irradiation externe précédant la biopsie et la curiepuncture, la curiepuncture ainsi que l'irradiation externe qui lui font suite, s'étale sur une durée de 25 à 40 jours maximum. C'est donc un traitement très étalé et important.

Les suites immédiates d'un tel traitement sont au point de vue local une vaste radiodermite exsudative du 2e degré avec chute de l'épithélium sur une surface correspondant à toute la zone aiguillée c-à-d. le sein et la région axillaire. Cette dermite est soignée simplement par lavages journaliers à l'eau oxygénée très diluée suivis d'application d'un onguent à base de vitamine A. Si la réparation, par suite d'infection, subit un temps d'arrêt, nous remplaçons la pâte à la vitamine A par un onguent qui contient 500 unités de pénicilline par gramme de corps gras. En cas d'évolution normale, la dermite est réparée après 6 à 8 semaines après la fin du traitement.

L'état général après un tel traitement est toujours légèrement affecté. Il existe à la fin de l'irradiation une anémie légère avec leucopénie. Ces conséquences de l'irradiation disparaissent assez rapidement et sont généralement effacées déjà avant la guérison complète de la dermite.

La peau, pendant les premiers mois après guérison de la dermite est mince, souple et non adhérente. Par après, suivant les personnes, il survient des signes de radiodermite chronique non ulcérée d'intensité

variable avec télangectasies ou des taches d'hyperchromie voisinant avec des taches d'achromie. Le derme peut présenter une sclérose progressive surtout autour des points d'implantation des aiguilles. Le sein lui-même dans les mois qui suivent le traitement, est généralement très souple, ne présentant aucun signe d'induration. Par après, généralement un an ou plus après le traitement, on voit survenir chez un certain nombre de femmes, en même temps que se développent des signes de dermite chronique, une sclérose profonde plus ou moins accentuée. La nature de cette induration est parfois bien difficile a interprêter. On hésite devant la possibilité d'une récidive ou d'une simple induration due à une sclérose profonde. Si cette induration ne s'étend pas, nous avons l'habitude de la considérer comme de la sclérose postradiothérapique. S'il en est bien ainsi, dans un bon nombre de cas on voit celle-ci s'assouplir progressivement dans les années qui suivent. S'il s'agit d'une récidive l'induration augmente et après un certain temps on n'hésite plus guère devant le diagnostic à poser. Nous tenons à faire remarquer que l'évolution de telles récidives en territoire irradié est particulièrement lente.

Devant la difficulté qu'il y a à diagnostiquer les récidives torpides ou latentes locales ou à distance, nous avons pris la décision pour établir nos statistiques de ne tenir compte que du nombre de malades en vie sans essayer de faire une discrimination entre ceux qui seraient ou ne seraient pas en puissance de récidive. Ceux qui présentent une récidive évolutive ne tardent pas à succomber au cours de l'année ou l'année suivante et les statistiques établies sur une longue période d'observation s'épurent ainsi d'elles-mêmes automatiquement.

Depuis 1931 nous avons donc traité par cette méthode 290 cas de cancers des types I et II de Steinthal et l'observation soigneuse de tous ces malades au cours de ces 16 années montre que les très longues survies sont nombreuses. Ainsi sur 216 malades traités depuis plus de 5 ans, 116, soit 53.6 %, sont en bonne santé, et sur 125 malades susceptibles d'avoir 10 ans d'observation 45 sont encore en vie après un tel laps de temps soit 36 %. Cela nous montre que si un certain nombre des indurations signalées plus haut sont des récidives, celles-ci doivent être particulièrement torpides et relativement inoffensives pour les malades, puisqu'elles permettent une aussi longue survie. (Voir tableau n° 1.)

L'observation de la courbe de mortalité nous montre d'ailleurs que le pourcentage des survies tout au long des 15 années d'observation est élevé. (Tableau n° 5.)

L'étude détaillée de certains éléments de cette statistique montre aussi que notre méthode de biopsie par enlèvement total d'une petite tumeur au bistouri électrique après irradiation préalable du sein par 750 r est sans danger. Ainsi nous avons relevé que parmi nos 125 malades qui sont susceptibles d'avoir 10 ans d'observation, 65 ont subi ce genre

Tableau N° 1.

C. du sein au 31. 12. 46. Catégorie: I et II Opérables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1931.....	9	8	8	7	6	5	4	4	4	4	3	3	3	3	3	3
1932.....	14	14	13	13	11	9	7	7	7	7	6	6	5	5	5	
1933.....	23	23	21	19	17	17	14	11	11	11	11	11	9	9		
1934.....	17	16	16	13	13	11	11	11	9	8	8	8	8			
1935.....	34	31	26	22	21	20	17	16	9	7	7	7				
1936.....	28	26	23	21	17	17	14	14	11	11	10					
1937.....	18	18	18	15	12	9	9	9	9	7						
1938.....	15	15	11	9	7	5	5	5	5							
1939.....	19	17	16	13	12	10	9	9								
1940.....	16	11	9	8	5	5	4									
1941.....	23	20	17	14	9	8										
1942.....	24	21	14	11	10											
1943.....	18	13	11	8												
1944.....	15	14	10													
1945.....	17	15														
Vivants	290	262	213	183	140	116	94	86	65	55	45	35	25	17	8	3
Total		290	273	258	240	216	193	177	158	143	125	97	63	46	23	9
% de vivants	%	90.4	78.0	70.9	58.3	53.6	48.7	48.5	41.1	38.4	36	36.0	39.6	36.9	34.7	33.3

d'intervention. Or 22 de ces malades sont encore en vie 10 ans révolus après le traitement, soit 33 %, alors que l'ensemble des 125 cas donne un pourcentage de 36 % de survie après ce même laps de temps.

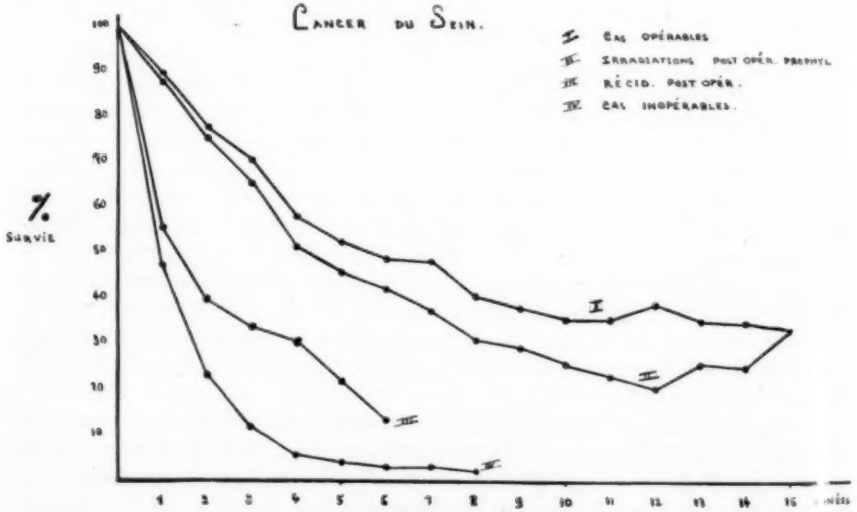

Tableau n° 5.

Cancers inopérables

Parmi cette catégorie nous avons rangé les cas des types III et IV de Steinthal c-à-d. des malades présentant outre des ganglions axillaires, de ganglions dans la région susclaviculaire ou dans l'aisselle opposée ainsi que tous les cas largement ensemencés à distance: à la peau, dans les os ou dans les plèvres. Nous n'avons refusé au traitement que les cas présentant des métastases hépatiques. En 15 ans nous avons pu traiter 23 de ces cas par les rayons seuls. Chaque fois que la chose fut possible ils ont reçu le traitement classique décrit plus haut et appliqué aux cas opérables. Les cas très avancés n'ont généralement reçu qu'un traitement incomplet sur le sein, parce que nous nous voyions contraints pour l'un ou l'autre motif tel que la douleur par exemple de concentrer notre action sur une région déterminée autre que le sein. Ce fut le cas pour les malades présentant des métastases osseuses importantes.

Ces métastases obéissent au traitement et les douleurs qu'elles provoquent retrocèdent sous son influence. Les doses sédatives contre les douleurs ne sont pas élevées. Dans des cas de vastes envahissements de la colonne et du bassin, il nous est arrivé de donner seulement 25 r à 50 r, 3 fois par semaine sur de très grands champs jusqu'à une dose totale de 500 à 750 r par région traitée et d'obtenir d'excellents effets sédatifs et même des recalcifications partielles. Quand on a affaire à une métastase osseuse unique, ce qui est rare, on peut donner à ce niveau des doses nette-

Tableau No 2.

C. du sein au 31. 12. 46. Catégorie: III et IV: Inopérables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1931.....	8	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0
1932.....	19	11	3	2	1	1	1	1	1	1	1	1	1	1	1	
1933.....	24	16	10	6	3	2	1	1	1	1	0	0	0	0		
1934.....	16	6	1	0	0	0	0	0	0	0	0	0	0			
1935.....	12	5	4	2	1	1	1	1	1	1	1	1				
1936.....	20	6	4	1	0	0	0	0	0	0	0					
1937.....	20	6	3	2	2	2	0	0	0	0						
1938.....	13	3	1	1	0	0	0	0	0							
1939.....	17	11	7	3	2	2	2	2								
1940.....	10	5	1	0	0	0	0									
1941.....	14	8	2	2	1	1										
1942.....	15	6	4	2	1											
1945.....	18	12	7	4												
1944.....	11	5	2													
1945.....	14	7														
Vivants	231	110	51	26	11	9	5	5	3	3						
Total		231	217	206	188	173	159	149	132							
% de vivants	%	47.6	23.4	12.1	5.8	4.6	3.2	3.3	2.2							

ment plus considérables allant jusque 1,500 et même 2,000 r mesurés dans l'air par région malade.

Les survies de telles malades, traitées pour la plupart à titre palliatif, sont peu considérables. Sur 173 malades susceptibles d'avoir 5 ans d'observation 9, soit 4.6 % sont en vie. Après 10 ans 2 malades sur 79 sont vivantes. Un cas est encore en vie et sans tumeur apparente 14 ans après le traitement. Si le nombre de survies importantes est très minime le fait de voir quelques rares cas en bonne santé après 5, 10 ans ou plus d'observation nous incite à ne pas abandonner ces malades à elles-mêmes et d'avoir le courage de les traiter. (Voir tableau n° 2.)

Cancers irradiés à titre prophylactique après Halsted

Depuis 1931 nous avons eu l'occasion d'irradier à titre prophylactique 287 malades. Celles-ci pour la très grande majorité nous ont été envoyées par nos collègues qui les avaient opérées ou par des médecins de diverses régions du pays: peu ont été opérées dans notre établissement. Pour beaucoup d'entre eux nous n'avons pu obtenir le résultat de l'examen microscopique. Au moment où nous les avons prises en traitement aucune d'entre elles ne présentait de signe de récidive. Il s'agissait donc de cas du type I et II de Steinthal sans qu'il nous ait été possible, par les renseignements obtenus, de pouvoir les diviser en cas du type I sans métastases axillaires et en cas du type II.

Nos techniques d'irradiation ont varié au cours de ces quinze années, nous ne croyons pas utile de les décrire toutes. Nous nous bornerons à parler de celle que nous employons encore aujourd'hui et que nous avons employée pour traiter la majorité de nos malades.

Nous commençons le traitement par l'irradiation d'un grand champ couvrant l'entièreté de l'hémithorax opéré, depuis le rebord costal jusqu'au sommet du creux sus-claviculaire. Le bras du malade est relevé, la main posée derrière la nuque et la tête tournée du côté opposé au côté irradié de façon à exposer le plus largement possible au rayonnement le creux axillaire ainsi que le creux sus-claviculaire. Nous irradions généralement sous une tension de 180 Kw avec un filtre de $^1/_2$ de cuivre, à une distance anti cathode-peau de 60 centimètres au moins. Nous donnons chaque jour une dose de 50 r mesurés dans l'air jusqu'à donner une dose totale de 500 à 750 r. Après cela nous prononçons généralement l'irradiation au niveau du creux sus-claviculaire et du creux axillaire. Ici nous utilisons une tension de 200 Kw et nous filtrons sur 1 de cuivre, donnant chaque jour une dose de 150 r mesurés dans l'air. La dose totale donnée au niveau de chacun des creux est d'habitude de 1,500 r mesurés dans l'air. Nous prononçons l'irradiation au niveau des creux et particulièrement au niveau du creux sus-claviculaire parce que c'est là les

os mis à part, que nous voyons survenir le plus fréquemment des récidives plutôt qu'au niveau de la peau qui recouvre l'emplacement du sein. Ce genre de traitement large mais étalé est généralement bien supporté. Nous croyons qu'il est important de ne pas utiliser des doses trop fortes pour ne pas altérer l'état général de la malade.

Les résultats sont a peu près du même ordre que ceux obtenus par le traitement radiologique sans opération des cas I et II. Après 5 ans 91 malades sur 196 sont vivantes et en bonne santé soit 46.4 %, après 10 ans 25 malades sur 95 vivent soit 26.3 %. Il est assez curieux de constater que les longues survies ont une tendance a être moins nombreuses que celles après traitement par les seules radiations. Il s'agit peut-être là d'une simple coïncidence provenant d'un nombre trop restreint de cas. Toutefois nous tenions à signaler la chose pour montrer une fois de plus que le traitement radiologique seul est loin d'empêcher les longues survies. (Voir tableau n° 3.)

Tableau No 3.

C. du sein au 31 12. 46. Catégorie: Irradiations postop. prophyl.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1931.....	12	10	10	9	8	8	7	7	6	5	4	4	4	4	4	4
1932.....	12	9	7	7	6	5	4	3	3	3	2	2	2	2	2	
1933.....	14	13	13	13	11	9	9	7	5	4	3	3	3	2		
1934.....	17	11	8	7	7	4	4	4	4	3	2	2	2			
1935.....	21	19	18	14	13	11	10	8	7	7	7	7				
1936.....	19	18	16	13	12	10	9	9	7	7	7					
1937.....	20	18	13	8	7	6	6	6	6	5						
1938.....	28	24	21	19	13	11	10	8	7							
1939.....	21	17	15	13	12	11	10	10								
1940.....	17	16	15	14	11	8	8									
1941.....	15	15	13	12	9	8										
1942.....	25	24	19	18	16											
1943.....	30	27	25	20												
1944.....	17	16	11													
1945.....	19	18														
Vivants	287	255	204	167	125	91	77	62	45	34	25	18	11	8	6	4
Total		287	268	251	221	196	181	164	143	115	95	76	55	38	24	12
% de vivants	%	88.8	76.1	66.5	52.0	46.4	42.5	37.8	31.4	29.5	26.3	23.6	20	21.0	25	33.3

Les récidives chirurgicales

Nous en avons soigné un très grand nombre, en moyenne 30 à 40 par an. Nous avons traité des cas extrêmement avancés. En fait nous n'avons refusé au traitement que les cas de métastases hépatiques. Le nombre de cas de métastases osseuses traités est particulièrement élevé. Dans la statistique de 205 cas que nous présentons, les cas les plus anciens remontent à 1940. Nous nous sommes limités à ce recul qui bien que peu

considérable est néanmoins suffisant pour montrer que les récidives chirurgicales ne sont point des cas entièrement perdus et qu'un traitement radiologique judicieusement conduit peut leur assurer une survie considérable, dépassant pour un nombre important de cas la limite des 5 ans jadis reconnue classique pour l'appréciation de la valeur d'un procédé thérapeutique en cancérologie. Ainsi sur les 69 cas ayant dépassé cette limite 17 sont encore en vie soit 24.6 %! (Tableau n° 4.) La technique à employer varie fortement d'après le genre de récidive et il faudrait un long article pour en traiter en détail. Qu'il nous suffise de dire que le traitement des récidives localisées se rapproche du traitement des cas de cancers primitifs et celui des cas avec métastases et notamment avec métastases osseuses est semblable à celui des cas primitifs présentant les mêmes complications. Une règle assez générale qui doit guider le traitement est celle qui consiste dans les cas de généralisation osseuse à ne pas donner des doses trop considérables qui altéreraient d'une façon irréparable l'état général de ces patients déjà souvent très compromis.

Tableau N° 4.

C. du sein au 31. 12. 46. Catégorie: Récidives postopératoires.

		1	2	3	4	5	6
1940.....	30	15	11	9	5	5	4
1941.....	39	27	21	17	15	12	
1942.....	24	17	12	9	9		
1943.....	40	20	13	10			
1944.....	36	21	11				
1945.....	36	16					
Vivants	205	116	68	45	29	17	4
Total		205	169	133	93	69	30
% de vivants	%	56.5	40.2	63.8	31.1	24.6	13.3

Traitement médical adjuvant du traitement radiologique

Comme on le sait il n'existe aucun traitement médical même simplement adjuvant qui soit vraiment efficace. Il existe pourtant des médicaments utiles au traitement et qui peuvent rendre des services.

Ainsi pour tous les cas nous avons l'habitude de conseiller au malade un régime reminéralisant, relativement pauvre en graisses et enrichi de vitamines du système B notamment la B_1, la B_2 et la nicotinamide.

Nous prescrivons un régime pauvre en graisses parce que beaucoup de données expérimentales montrent qu'un bon nombre de graisses favorise la genèse et l'évolution de ces cancers.

Nous enrichissons le régime de nos malades en système B parce que la cellule cancéreuse brûle mal ses hydrates de carbone et que la B_1, la B_2

et la nicotinamide font partie intégrante des groupements prosthétiques de divers enzymes intéressées dans le métabolisme des sucres. De plus la B_1, l'après des recherches récentes, prend part dans le foie à la neutralisation des hormones sexuelles qui selon toute vraisemblance jouent un rôle important dans l'évolution du cancer du sein.

Pour favoriser la fixation du calcium nous donnons volontiers un supplément de vitamine D. Dans les cas de métastases osseuses avancées nous enrichissons fortement le régime en calcium et nous donnons facilement jusque 600,000 unités par mois ou même par quinzaine.

La vitamine A est utile à dose modérée comme tonique général.

Dans les cas avancés nous nous servons souvent de transfusions à doses modérées: 300 à 500 cc par semaine. Souvent cette médication est d'un appoint précieux et permet aux malades de supporter un traitement déprimant qui n'eut pas été possible sans elle.

Nous proscrivons dans toute la mesure du possible l'emploi d'analgésiques de toute nature qui à notre avis sont contre-indiqués pour de multiples raisons chez ces malades qui souffrent d'une carence de fixation d'oxygène.

Stérilisation et hormones comme adjuvant dans le traitement du cancer du sein

Les anciens chirurgiens recommandaient déjà la castration chirurgicale comme adjuvant du traitement du cancer du sein. Depuis l'avènement de l'ère radiologique la castration roentgénienne a été recommandée par divers auteurs. Nous l'avons recommandée nous-mêmes dès 1938. Nous n'avons pas changé d'avis, elle nous paraît logique pour diverses raisons.

L'étude du cancer expérimental de la mamelle chez la souris et le rat a montré que la folliculine était un facteur déterminant important dans la genèse et l'évolution de ces cancers. Les souris mâles appartenant à une race dont les femelles font spontanément du cancer, n'en font néanmoins jamais sauf si on les injecte de folliculine. Si on injecte les femelles, elle font leur cancer beaucoup plus tôt et avec un pourcentage bien plus considérable. La plupart des souris femelles castrées avant la puberté, même appartenant à des races à hérédité chargée, ne font plus de cancer mammaire. Les souris de certaines races castrées très tôt après la naissance en font quand même mais alors c'est parce que leur capsule surrénale par une sorte de vicarience fonctionelle secrète des hormones oestrogènes.

Si l'on interroge soigneusement les femmes porteuses d'un cancer du sein, particulièrement celles souffrant d'un cancer du type inflammatoire et qui ne sont pas encore ménopausées, elles accusent régulièrement des poussées évolutives quelques jours avant leurs époques.

Ces diverses données cliniques et expérimentales permettent de penser que les hormones oestrogènes chez la femme doivent jouer un rôle favorisant dans la genèse des cancers du sein. Logiquement la suppression de la fonction ovarique semble donc recommandable chez les femmes atteintes de ce type de cancer. Il est difficile de déterminer quel genre de castration, chirurgicale ou radiologique, paraît le plus recommandable. Il est un fait qu'il y a une différence évidente au point de vue physiologique entre les deux procédés, la castration radiologique laissant persister le stroma de la glande et aux dépens de celui-ci peuvent se différencier des cellules à caractères fonctionnels jouant le rôle de glande interstitielle. Récemment A. SICARD a publié un travail où il montre que la castration chirurgicale aurait encore une action inhibante évidente chez des malades ayant subi au préalable une castration radiologique. La douleur due à des métastases osseuses serait particulièrement influencée.

La castration radiologique d'après de nombreux auteurs a néanmoins elle aussi une action inhibante sur le cancer du sein. (HAELBERSTAEDTER, NATHANSON, MAISIN et d'autres.)

Si la suppression de la fonction oestrogène a une influence favorable, il est logique de songer à employer dans un but thérapeutique l'hormone antagoniste c-à-d. la testostérone. Dès 1939 nous l'avons employée dans le traitement des métastases osseuses et d'autres auteurs l'ont utilisée dans un même but. Il est très difficile de tirer de ces travaux des conclusions fermes quant à l'action d'un tel traitement; on a l'impression clinique que dans quelques cas il s'agit d'un traitement palliatif efficace contre la douleur tout au moins.

Des résultats plus difficiles à expliquer sont ceux que l'on obtient par l'emploi du propionate de stilboestrol en implantation sous-cutanée à la dose de 100 ou 200 milligrammes par comprimé, chaque comprimé permettant une résorption de 0.3 milligramme environ par jour. Nous avons vu, dans certains cas, des tumeurs ulcérées se cicatriser pendant un certain temps et des métastases osseuses du type ostéoclasique regresser ou disparaître sans autre thérapeutique. Dans un cas toujours vivant et actuellement en observation, présentant de nombreuses métastases ostéolytiques de la calotte cranienne, nous avons vu ces métastases disparaître pendant que d'autres apparaissaient dans d'autres os. Ce sont là des faits actuellement bien difficiles à expliquer scientifiquement. Le pourcentage de cas qui répondent à cette thérapeutique n'est pas élevé, on l'a estimé à 5 %. D'après notre expérience il pourrait être plus élevé, mais il nous est impossible d'avancer des chiffres exacts parce que le nombre de cas que nous avons soignés exclusivement par cette méthode est peu élevé. On a prétendu également que les personnes âgées au delà de 60 ans répondaient le mieux à cette thérapeutique. Il se peut que ce soit exact mais nous pouvons affirmer avoir vu deux cas présentant des

métastases osseuses et agés de moins de 40 ans répondre à ce traitement. Par contre nous devons à la vérité de dire que nous avons vu des cas jeunes et vieux empirer par l'emploi du distilbène. C'est donc là une thérapeutique délicate.

Parmi les malades «opérables» et parmi celles traitées prophylactiquement après Halsted nous avons systématiquement procédé à la stérilisation ovarique des femmes non encore ménopausées. Par contre nous n'avons jamais utilisé chez elles le distilbène et ce n'est qu'exceptionnellement et très temporairement que nous avons parfois utilisé la testostérone. Nous avons réservé l'emploi de ces méthodes à de mauvais cas de récidives chirurgicales ou a des cas primitifs porteurs de métastases généralisées.

Discussion des résultats

Nous aimerions, dans l'appréciation de nos résultats, être scrupuleusement objectifs car le problème est important et mérite d'être traité avec précision.

Ne considérant que nos propres séries nous pouvons en comparer deux entre elles avec grand fruit et en tirer des conclusions: nous voulons parler de nos cas du type I et II de Steinthal traités uniquement par les radiations et nos cas traités prophylactiquement après opération de Halsted. Ces derniers sont aussi des cas I et II puisque au moment de leur prise en traitement par nous ils ne présentaient aucune métastase cliniquement décelable en dehors du territoire opéré. Ils seraient en tous points comparables à nos cas I et II traités radiologiquement si nous possédions une analyse microscopique de tous les cas. Malheureusement ce sont tous des malades opérés ailleurs que chez nous et nous n'avons pu nous procurer le résultat de l'examen microscopique que pour 48 cas sur 196 susceptibles d'avoir cinq ans d'observation.

Si nous suivons le sort de ces 48 cas, nous voyons qu'après cinq ans 22 sont en vie soit 45.8 %. Tous les cas susceptibles d'avoir 5 ans, soit 196 comprenant donc ceux dont nous possédons l'examen microscopique, soit 48 ainsi que les autres, donnent après ce laps de temps 46.4 % de malades en vie. Les deux groupes — avec et sans biopsie — donnent donc des résultats semblables après 5 ans, ce qui semble indiquer que les cas dont nous ne possédons pas de biopsie étaient bien des cancéreux. Nous pouvons donc les considérer tous comme cancéreux et en ce faisant, nous ne pouvons que nous tromper à notre désavantage en plaçant la série des cas traités radiologiquement dans une situation désavantageuse. Or en comparant les courbes de mortalité des deux séries nous constatons que tout au long de nos 16 années d'observation toujours la courbe des cas traités par la radiologie seule indique pour ceux-ci

une survie supérieure à celle des cas traités prophylactiquement après Halsted. Nous pouvons donc affirmer que le traitement radiologique seul tel que nous l'avons conçu donne des résultats au moins comparables à ceux donnés par l'opération de Halsted suivie d'irradiation prophylactique. C'est là une conclusion importante. Jusqu'ici en effet, on n'a guère pratiqué le traitement radiologique seul et il existe peu de statistiques importantes de cas traités systématiquement de façon efficace par cette méthode. Ces résultats pensons-nous aideront grandement le traitement radiologique des cancers du sein (curiepuncture et radiothérapie externe combinées) a conquérir ses droits de cité comme traitement efficace et même classique.

Il nous est difficile de comparer nos résultats avec ceux de la chirurgie. Nous ne disposons pas de statistiques chirurgicales personnelles. Il en existe toutefois de très nombreuses dans la littérature. Malheureusement elles ne sont guère comparables et les résultats qu'elles apportent sont souvent très dissemblables. A titre d'exemple nous en citerons quelques uns.

Chirurgie seule, % de cas vivants après 5 ans.

Auteurs	Nombre de cas	Type II	Tous types réunis
Lewis et Rienhoff	420	—	18 %
Trout	152	—	22 %
Bucholz	121	—	22.3 %
Klingenstein	57	17 %	23 %
Hintze	—	—	30.1 %
Ducuing	121	—	31.4 %
Harrington	1,911	25 %	33.1 %
Gould	151	22 %	33.1 %
Moschowitz	89	—	34 %
Wintz	727	—	35 %
White	157	—	36 %
Lane-Claypton	2,006	—	37.4 %
Kiel	175	—	38.6 %
Lynham	—	—	40 %
Abell	217	26 %	44 %
Redman	106	41 %	46 %
Jessop	216	30.5 %	48 %

Si nous les considérons comme exacts et nous n'avons aucune raison de ne point le faire, nous nous voyons obligés de constater que les résultats du traitement radiologique seul sont au moins aussi favorables, nous pouvons même dire meilleurs. C'est là une conclusion qui, nous nous en rendons compte, ne sera pas aisément admise. Nous pensons toutefois que les résultats que nous apportons obligeront tous les travailleurs

objectifs à ne plus écarter sans plus, le traitement radiologique parce que moins efficace que l'opération de Halsted.

Un autre point important à discuter c'est la valeur comparative de la chirurgie employée seule et celle de la chirurgie suivie d'irradiation prophylactique. Cette question a fait l'objet de multiples discussions.

Nous pensons que pour clarifier le sujet il est bon de considérer à part les résultats chirurgicaux pour les cas du type I et ceux du type II. Pour les cas du type I c-à-d. ceux où l'examen microscopique des ganglions axillaires ne révèle la présence d'aucune métastase, la tumeur primitive étant petite et bien limitée au sein, la plupart des auteurs sont d'accord pour dire que les résultats après 5 ans sont très bons. GREENOUGH et SIMMONDS signalent 52 % de survies après 5 ans, LEE 72 %, HARRINGTON 71.2 %. Les pourcentages de TAILHEFER sont voisins. HARRINGTON mentionne de plus 52.9 % de survies après 10 ans et 40.7 % après 15 ans. Si on a affaire à des cas très limités de cet ordre, où l'opération de Halsted dépasse largement la zône envahie par le cancer, il semble que l'irradiation postopératoire ne doive apporter que peu d'appoint à la chirurgie. Qu'il nous soit permis de remarquer toutefois qu'une opération très large pour des cas si limités n'est pas capable de guérir tous les cas puisque la moitié environ succombent en 10 ans. C'est pourquoi nous comprenons que certains auteurs irradient quand même les cas du type I. Nous comprenons aussi qu'il doive être difficile d'apprécier la grandeur de l'appoint apporté à la chirurgie par la radiothérapie, les succès de la chirurgie seule étant élevés, l'amélioration résultant de la radiothérapie ne peut être que peu considérable.

Pour les cas du type II la question est différente. Ici les résultats chirurgicaux sont relativement médiocres puisqu'ils vont après 5 ans de 17 % à 41 % avec une moyenne de 27.9 %. En 1938 PFAHLER a publié un tableau des résultats des cas du type II opérés et irradiés prophylactiquement: ils vont après 5 ans de 27 % (WEISSWANGE) à 53 % (LEE) avec une moyenne de 39.6 %, ce qui représente par rapport aux résultats de l'opération seule un gain de 12 % environ, ce qui n'est pas négligeable.

Si l'on considère tous les cas opérés réunis, quel que soit le type, et irradiés prophylactiquement nous constatons ici aussi un gain d'environ 12 %. Voici d'ailleurs, réunis en un tableau, les principaux résultats que nous avons pu rassembler.

Devant un nombre aussi important de cas traités et longuement observés par les radiologues de tous les continents, il nous paraît logique d'admettre que l'irradiation post-opératoire constitue un appoint sérieux dans le traitement des cancers du sein. Nos résultats (46.4 % après 5 ans) viennent à l'appui de cette opinion. Nous tenons à répéter que ce groupe de cas n'a pas été selectionné par nous pour l'irradiation, mais par des

Auteurs	Nombre des cas	Pourcentage tous cas réunis	Auteurs	Nombre de cas	Pourcentage tous cas réunis
Hohhman.....	82	30.5 %	Gäbel et Magens ...	—	47.7 %
Nicolson et Berman	74	36.8 %	Holfelder	118	50 %
Westermark.....	70	37 %	Gratzek et Stenstrom	254	51 %
Matheros	153	37.8 %	Pfahler et Vastiné.	269	52.4 %
Billich.....	164	39.6 %	Hintz	183	53 %
Lee	217	41 %	Weisswange	171	53.7 %
Webster	358	42 %	Lynham	—	56 %
Portman	103	42.7 %	Wintz	727	59.9 %
Kiel	309	43.7 %	Hummel	115	68.7 %
Maisin	196	46.4 %			

collègues qui très généralement nous les ont envoyés parce qu'il s'agissait de cas du type II très caractérisés et qu'ils craignaient une récidive.

L'efficacité des radiations dans le traitement des cancers du sein nous paraît par ailleurs démontrée par les relativement très bons résultats que l'on obtient dans le traitement des récidives chirurgicales: 24.6 % de survie après 5 ans et aussi par les résultats obtenus dans le traitement de cas du type III et IV de Steinthal: 9 cas vivants sur 173 après 5 ans! Stenstrom pour un groupe de cas semblable signale même 8 survies sur 82 après 5 ans soit 10 %!

I. T. Nathanson et C. E. Welch ont établi une courbe de survie pour 100 cas de cancers du sein non traités, ils arrivent à dire qu'après 5 ans environ 18 % de ces cas sont encore vivants et après 10 ans environ 5 %. D'après ces chiffres nous pourrions validement conclure pensons-nous que certains de nos traitements du cancer du sein prolongent nettement la vie de nos malades, nous voulons surtout parler du traitement combiné chirurgie-irradiation post-opératoire et traitement radiologique seul (curiepuncture + rayons roentgen).

Nous n'avons pu dans ce travail discuter la valeur de traitement radiologique pré-opératoire parce que nous ne disposons pas de statistiques personnelles pour ce groupe de cas.

Enfin pour terminer cette discussion nous voudrions parler des avantages et des désavantages du traitement radiologique employé seul.

Un de ses plus grands avantages c'est de conserver le sein. Cet avantage est particulièrement apprécié par les malades qui systématiquement choisissent ce mode de traitement si on leur laisse le choix en disant que les résultats sont de même ordre que ceux de la chirurgie.

Parmi les désavantages il faut citer la longueur du traitement radiologique et la durée de la convalescence au cours de laquelle la malade

est astreinte à soigner la radiodermite du second degré qu'elle présente au niveau du sein.

Après le traitement, les séquelles de dermite chronique plus ou moins apparentes suivant les malades, sont pensons-nous un inconvénient mineur. Les malades sont très contentes d'avoir pu conserver leur sein malgré cet inconvénient.

Il est juste de signaler aussi que le traitement radiologique seul n'est pas facile à faire. Il doit l'être par un radiologue expérimenté. De plus la quantité de radium nécessaire pour un bon traitement est toujours importante.

Nonobstant ces inconvénients, les résultats très encourageants que nous avons présentés permettent pensons-nous de considérer cette méthode de traitement comme une méthode de valeur comparable au traitement combiné chirurgie-radiation et vraisemblablement meilleure que la chirurgie seule.

RÉSUMÉ

L'auteur présente les résultats obtenus à l'Institut du Cancer de Louvain dans le traitement de divers types de cancers du sein couvrant une période de 15 années. Les méthodes employées ont été le traitement exclusif par les radiations ou le traitement radiologique appliqué après opération de Halsted. Les résultats concernant l'irradiation post-opératoire viennent confirmer ceux de la plupart des auteurs. Ils montrent que les résultats chirurgicaux sont nettement améliorés par l'irradiation post-opératoire. Le traitement radiologique seul, sous forme d'une large curiepuncture combinée à une irradiation externe par rayons roentgen ou la télécuriethérapie, est une méthode qui donne des résultats au moins aussi bons que l'irradiation combinée à la chirurgie. On peut obtenir des survies très importantes par le traitement radiologique des récidives chirurgicales. Les cas inopérables donnent un très faible pourcentage de survie au delà de 5 ans.

SUMMARY

The author examines the results obtained at the Cancer Institute of Louvain in the treatment of different carcinoma mammae types, being carried out within 15 years. Used methods are reported to be either exclusive irradiations or irradiation treatment administered after Halsted operation. His results concerning post-operative irradiation concur to confirm mostly those of preceding authors. Surgical results are shown to be greatly improved by post-operative irradiation. Irradiation treatment by itself, given in large radium puncture, combined either to roentgen irradiation or to teleradium, proved to be a method permitting at least as good results as irradiation accompanying surgical treatment. A high rate of survival may be obtained by submitting surgical recurrences to roentgen therapy. Inoperable cases give a very low percentage of survival of more than 5 years.

ZUSAMMENFASSUNG

Verf. legt die Ergebnisse vor, die in einer Zeitspanne von 15 Jahren im Krebsinstitut zu Löwen bei der Behandlung von verschiedenen Typen von Brustkrebs erhalten wurden. Die benutzten Methoden waren Behandlung mit Bestrahlungen allein oder radio-

logische Therapie nach der Halsted'schen Operation. Die Ergebnisse der postoperati en Bestrahlung bestätigen diejenigen der Mehrzahl der Autoren. Sie zeigen, dass die Re ul- tate chirurgischer Behandlung durch die postoperative Bestrahlung wesentlich er- bessert werden. Die ausschliesslich radiologische Behandlung, in Form einer gro en Radiumpunktion, kombiniert mit Röntgenbestrahlung oder mit Fernbehandlung nit Radium, ist eine Methode, die mindestens ebensogute Resultate gibt, wie die nit chirurgischem Eingriff kombinierte Bestrahlung. Durch radiologische Behandlung der chirurgischen Rezidive lässt sich eine sehr bedeutende Prozentzahl Überlebender erzi en. Von den inoperablen Fällen überleben sehr wenige mehr als 5 Jahre.

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AUS DEM RÖNTGENINSTITUT UND DER RADIOTHERAPEUTISCHEN KLINIK DER UNIVERSITÄT ZÜRICH (DIR.: PROF. DR. H. R. SCHINZ)

DIE ABHÄNGIGKEIT DER PROGNOSE DER MAMMA-CARCINOME VOM TUMORSTADIUM UND VOM LEBENSALTER ANHAND VON 702 FÄLLEN[1]

von

H. R. Schinz und *Ch. Botsztejn*

Die Frage der exakten Prognosestellung beim Mamma-Carcinom beschäftigt immer wieder Chirurgen und Radiologen und ist Gegenstand zahlreicher Publikationen. Die Beurteilung der Lebenserwartung im Einzelfalle ist nicht nur an sich wichtig, sondern sie kann für die Wahl der Therapie von ausschlaggebender Bedeutung sein. So wird in der Regel bei Annahme einer schlechten Prognose von eingreifenderen operativen und strahlentherapeutischen Massnahmen Abstand genommen und nur eine palliative Behandlung durchgeführt. Es kommt immer wieder vor, dass der Hausarzt in ungenauer Kenntnis der Prognose dem Patienten eine Erfolgschance entzieht, indem er ihn dem Therapeuten überhaupt nicht zuweist, oder dass der Therapeut selber von vorne herein auf eine Erfolg versprechende Therapie aus gleichen Überlegungen verzichtet. Leider ist es zu wenig allgemein bekannt, dass die Carcinomprognose durch die Kombination der operativen und der Strahlentherapie (sei es Vor- und Nachbestrahlung, sei es Nachbestrahlung allein) und durch die alleinige Strahlentherapie wesentlich verbessert wurde.

Selbstverständlich wird die Prognose des Mamma-Carcinoms in erster Linie durch das *Tumorstadium*, d. h. durch die Ausdehnung des Tumors in der Brust und deren Umgebung und durch das Vorhandensein, die Lokalisation und die Ausbreitung der Metastasen beeinflusst. Es ist deshalb von grosser Bedeutung, über ein System der Stadieneinteilung zu verfügen, welches den zu beurteilenden Einzelfall in eine möglichst prognostisch einheitliche Gruppe einzuordnen erlaubt. Die Einteilung in grosse, und deshalb sehr heterogene Gruppen erlaubt keine genaue Prognosestellung.

[1] Bei der Red. am 6. V. 1947 eingegangen.

Neben dem Tumorstadium werden für die Prognose des Mamma-Carcinoms noch andere Faktoren verantwortlich gemacht, die in ihrer Wichtigkeit von verschiedenen Autoren verschieden gewertet werden. Diese Faktoren sind:

1. Die Wachstumsgeschwindigkeit des Tumors, d. h. das Verhältnis des Tumorstadiums zur Anamnesendauer,
2. Die histologische Struktur des Tumors, vor allem der Reifegrad der Tumorzellen, wobei die unreiferen Formen als besonders bösartig gelten,
3. Das Alter der Patientin. Es wird allgemein angenommen, dass die Prognose umso schlechter wird, je jünger die Frau ist,
4. Die Koinzidenz des Tumors mit Gravidität und Laktation.

In dieser Arbeit haben wir uns zur Aufgabe gemacht, den Einfluss des Tumorstadiums auf die Prognose des Mamma-Carcinoms anhand unseres relativ grossen Materials zu untersuchen; ferner untersuchen wir die heute besonders aktuelle Frage der Bedeutung des Lebensalters. Die Überlegung, dass die Bösartigkeit des Mamma-Carcinoms bei jugendlichen Frauen im Zusammenhang mit der Ovarialfunktion steht, führte unter anderem vielerorts zur Ausübung einer Röntgensterilisation als zusätzliche Therapie. Neuerdings wird auch versucht, durch hormonale Umstimmung mit androgenen Stoffen das Tumorwachstum zu hemmen. Da diese Massnahmen einen tiefen Eingriff, sowohl in körperlicher, als in psychischer Hinsicht in die Persönlichkeit einer jungen Frau bedeuten, konnten wir uns zur Sterilisation nicht entschliessen, ohne den Beweis dafür zu besitzen, dass die Mamma-Carcinome bei jungen Frauen tatsächlich ungünstig verlaufen.

Unser Material aus den Jahren 1919—1945 besteht aus 1033 Malignomen der Brustdrüse. Im Gegensatz zu chirurgischen Kliniken verfügen wir über ein sehr heterogenes Material, worunter sich zahlreiche Fälle befinden, die uns erst mit Metastasen oder Rezidiven zur Bestrahlung zugewiesen werden, oder bei denen die Vorgeschichte und vor allem das Tumorstadium vor der Operation nicht mehr zu rekonstruieren sind. Deshalb kommen für die vorliegende statistische Zusammenstellung 318 Fälle in Wegfall. Ferner werden auch 13 Mamma-Sarkome nicht berücksichtigt. Doppelseitige Tumoren (einfach gezählt) sind in den 702 analysierten Fällen inbegriffen. Interkurrent gestorbene und verschollene Patienten wurden als Carcinomsterbefälle gerechnet.

Stadieneinteilung

Da die hauptsächliche und gleichzeitig die älteste Therapie des Mamma-Carcinoms die Radikaloperation ist, richten sich die gebräuchlichen

Stadienteinteilungen nach dem chirurgischen Kriterium der Operabilität, das eigentlich ein topographisch-anatomisches ist. Die älteste und am häufigsten angewandte Einteilung nach STEINTHAL wurde von vielen Seiten als zu summarisch betrachtet und erfuhr, vor allem durch Radiologen, im Laufe der Zeit zahlreiche Modifikationen (ANSCHÜTZ, JÜNGLING). Leider werden auch diese erweiterten, auf dem Schema von Steinthal basierenden Einteilungen der Mannigfaltigkeit der Mammacarcinome bezüglich der Ausdehnung des Primärtumors und der Metastasen nicht vollständig gerecht. Deshalb hat jede Klinik ihre eigene Stadieneinteilung, die zwar nach Steinthal benannt wird, aber mit Einteilungen anderer Kliniken nicht ohne weiteres vergleichbar ist, weil die Grenzen zwischen den Stadien verschieden gezogen werden. Die Radiotherapeutische Klinik Zürich bildet in dieser Hinsicht keine Ausnahme. In Anlehnung an die Stadieneinteilung von Tumoren der oberen Luft- und Speisewege werden die Mamma-Carcinome nach folgendem, von SCHINZ 1933 aufgestelltem Schema klassifiziert:

Stadien-Einteilung der Mamma-Tumoren

1. Primärtumor.

Stadium:

I Kleiner, einige cm. bis pflaumengrosser Primärtumor, der ganz in der Drüse liegt und weder mit der Haut, noch mit der Unterlage verwachsen ist. Der Primärtumor ist technisch und prognostisch sehr gut operabel.

II Der Primärtumor ist hühnereigross oder grösser. Die Beweglichkeit gegenüber der Subkutis oder gegenüber dem Pektoralis ist nicht mehr ganz frei. Der Primärtumor ist technisch und prognostisch operabel.

III Der Primärtumor ist entweder gegen die Haut, gegen den Pektoralis oder gegen beide fixiert und kann in geringem Umfange ulceriert sein. Der Primärtumor ist technisch operabel, prognostisch inoperabel.

IV Der Primärtumor ist mit der Brustwand verbacken, unverschieblich oder breit ulceriert. Der Primärtumor ist auch technisch inoperabel. Fälle mit Lymphangitis carcinomatosa der Haut.

2. Metastasen.

0 Keine Lymphknoten nachweisbar.

a Keine klinisch feststellbaren Metastasen. Kleine Lymphknoten palpabel, aber nicht suspekt.

b Die Lymphknoten sind deutlich vergrössert, sie sind aber gut verschieblich. Es sind höchstens 2—3 Lymphknoten nachweisbar. Die Lymphknoten sind operabel.

c Die Lymphknoten sind gegen die Umgebung fixiert oder wenn Fixationserscheinungen fehlen, so ist doch die Lymphknotenstation mit Metastasen ausgefüllt. Die Lymphknoten sind prognostisch inoperabel.

d Die Lymphknotenmetastasen sind unverschieblich und eventuell durch die Haut durchgebrochen. Die Lymphknoten sind technisch inoperabel.

e Fernmetastasen.

h Hautmetastasen.

3. Anwendung der Stadieneinteilung und des Metastasenbefundes in einer Formel und Erläuterung derselben.

Zuerst wird das Stadium des Primärtumors angegeben, dann die Stadien der homo- und kontralateralen Lymphknotenstationen in der Reihenfolge: *axillär, infraklavikulär, supraklavikulär,* Fernmetastasen, Hautmetastasen.

Je nachdem welche Gebiete, lokal oder regionär, befallen sind oder nicht, resultiert die Formel, z. B. bei kontralateral negativem Befund:

II bab + aaa

bei kontralateral positivem Befund:

II bab + bba

Bei Befallensein beider Mammae wird das Stadium für jede Seite angegeben, z. B.: rechts II bab + links I aaa, wobei das schwerere Stadium an erster Stelle steht.

Diese Stadieneinteilung basiert bei inoperablen Fällen ausschliesslich auf dem klinischen Befunde, bei operablen Fällen, die zur Operation kommen, und bei denen ein einwandfreier pathologisch-anatomischer Bericht eingeht, muss die klinische Stadieneinteilung revidiert und rektifiziert werden. Es kommt vor, dass z. B. axilläre Lymphknoten vor der Operation die Bezeichnung a erhalten haben, aber in die Gruppe b wandern in dem Moment, wo im histologischen Präparat carcinomatöse Infiltrate nachweisbar waren, oder es kann auch umgekehrt sein.

Was die Fernmetastasen anbetrifft, so handelt es sich um haematogene Metastasen, die wir in einer Gruppe zusammenfassen, unbekümmert darum, ob es sich um die Lungen, das Knochensystem oder andere Organe handelt. Was die Hautmetastasen anbetrifft, so werden zu haematogenen Metastasen nur solche gerechnet, die weit vom Sitz des Primärtumors entfernt sind. Die anderen sind im Primärstadium enthalten.

Unser Schema hat den Vorteil des Übersichtlichkeit durch die Trennung des Stadiums des Primärtumors von dem der Metastasen und erlaubt deshalb, den Einzelfall genau zu umschreiben und exakt einzuordnen. Es hat sich im klinischen Gebrauch besonders zur Bestimmung der einzuschlagenden Therapie und der Dosierung bei der Bestrahlung sehr gut bewährt. Das Schema erlaubt auch einen Vergleich mit Erfolgsstatistiken anderer Kliniken, indem die einzelnen kleinen Gruppen sich mühelos in ein beliebiges Schema zusammenlegen lassen. Der grosse Nachteil ist die starke Zersplitterung des Materials in eine enorme Zahl von Kombinationen. Wir haben daher für die Beurteilung der Prognose unsere nach obigem Schema klassifizierten Fälle in 8 Gruppen zusammengefasst:

Gruppe 1, Stad. I aaa + aaa d. h. ganz kleine Tumoren ohne jegliche Metastasen.
» 2, » II aaa + aaa d. h. grössere, aber gut operable Tumoren ohne jegliche Metastasen.

Gruppe 3, Stad. III aaa + aaa d. h. grosse, technisch noch operable Tumoren, ohne jegliche Metastasen.

» 4, Stad. I und II baa + aaa d. h. gut operable Tumoren mit axillären kleinen Metastasen.

» 5, Stad. I und II mit mehr als axillären Metastasen vom Stad. b, Stad. III mit regionären Metastasen,
doppelseitige Tumoren vom Stad. I, II und III, und Tumoren vom Stad. I, II und III mit kontralateralen Lymphknotenmetastasen oder mit Hautmetastasen der Mamma-Gegend,
(d. h. sämtliche Tumoren vom Stad. I, II und III, die nicht in die Gruppe 1, 2, 3, 4 passen, ausgenommen Tumoren mit supraklav. Metastasen, Metastasen vom Stad. d und Fernmetastasen.)

» 6, Tumoren der Gruppe 1 bis 5 mit supraklavikulären Metastasen vom Stadium b oder c (operable Metastasen).

» 7, Stad. IV mit oder ohne regionären Metastasen und Tumoren vom Stadium I, II und III mit regionären Metastasen vom Stadium d (inoperabel).

» 8, Alle Tumoren mit Fernmetastasen.

Um Verwechslungen der Gruppe mit den Stadien des Primärtumors auszuschalten, erfolgt die Gruppenbezeichnung immer mit arabischen Ziffern, die Stadieneinteilung immer mit römischen Ziffern.

Einfluss des Tumorstadiums auf die Überlebensdauer

In Tabelle 1 haben wir die Überlebensdauer unserer 702 Fälle zusammengestellt. Die Fälle sind nach dem Schema von SCHINZ klassifiziert und in 8 oben angeführte Gruppen zusammengefasst.

Übersichtlicher als in der Tabelle sind die Prozentzahlen der Überlebenden der einzelnen Gruppen im Vergleich mit der normalen Absterbekurve von 55 jährigen Frauen, entsprechend dem Durchschnittsalter unserer Fälle, der aus Abb. 1 zu ersehen ist.

Wir sehen aus diesen Darstellungen, dass die Einteilung in 8 Gruppen eine ziemlich genaue Prognose gestattet, indem die Prozentzahl der Überlebenden nach 3 Jahren in gleichmässigen Abständen von 5—10 % von Gruppe zu Gruppe sinkt; bei der 5 jährigen Überlebensdauer sind die Differenzen etwas grösser. Ein Blick auf die zum Vergleich aufgestellte Tab. 2 und Abb. 2 wo das gleiche Material in Steinthalstadien zusammengelegt wurde (wobei Steinthal I = Gruppe 1, Steinthal II = Gruppe 2, 3, 4, Steinthal III = 5, 6, 7 ist), zeigt den grossen Vorteil der differenzierten Stadieneinteilung.

Während z. B. die summarische Gruppe Steinthal II eine 5 jährige Überlebensdauer von nur 48 % aufweist, erlaubt uns unsere Gruppeneinteilung einer Patientin vom Stad. II aaa (Gruppe 2), welches auch zum Stadium Steinthal II gehört, 67 % Chancen auf 5 jährige Lebensdauer vorauszusagen. Die Kurven der einzelnen Gruppen Abb. 1 verlaufen ziemlich parallel, die Prognose verschlechtert sich von Gruppe

zu Gruppe sukzessiv. Eine Ausnahme bilden Gruppe 3 (Stad. III aa.) und Gruppe 4 (Stad. I baa und II baa), deren Kurven von Überlebenden sich teilweise überdecken. Die Tatsache ist bemerkenswert, weil die zwei Gruppen ganz verschiedene Fälle enthalten: bei Stad. III aaa sind es lokal sehr ausgedehnte Tumoren, mit Einwucherung in die Haut, teilweise Fixierung auf der Unterlage oder geringer Ulzeration, d. h. Tumoren an der Grenze der Operabilität; beim Stad. I baa und II baa sind es kleine, umschriebene Tumoren mit kleinen axillären Metastasen, d. h. durchaus radikal operable Fälle. Die relativ gute Prognose der Gruppe 3 ist vor allem auf den Beitrag der Bestrahlung (Vor- und Nachbestrahlung oder Nachbestrahlung allein) zur Therapie des Mammacarcinoms zurückzuführen, da diese Tumoren nach chirurgischen Kriterien eigentlich zum grossen Teil zum Stadium Steinthal III gehören sollten. Dass

Tab.

Überlebensdauer von 702 Fällen von Mamma-

	Zahl der Fälle	Durchschnittsalter in Jahren	Es lebten			
			1 J.		2 J.	
			abs.	%	abs.	%
Gruppe 1	58	52.2	57/58	98.3	49/52	94.2
» 2	95	55.0	94/95	99.0	80/88	90.8
» 3	39	60.6	35/39	89.9	24/29	81.7
» 4	171	51.2	155/171	90.5	127/162	78.0
» 5	165	55.7	130/165	78.8	90/145	58.5
» 6	43	52.2	35/43	81.4	18/41	44.0
» 7	93	60.4	43/93	46.2	16/86	18.6
» 8	38	53.5	9/38	23.6	2/35	5.7
Total	**702**	**54.8**	**558/702**	**79.5**	**406/639**	**63.6**

Tab.

Überlebensdauer von 702 Fällen von Mamma-

Stadien	Zahl der Fälle	Durchschnittsalter in Jahren	Es lebten			
			1 J.		2 J.	
			abs.	%	abs.	%
Steinth. I (Gruppe 1)	58	52.2	57/58	98.3	49/52	94.2
» II (Gruppe 2, 3, 4)	305	53.9	284/305	93	231/280	82.5
» III (Gruppe 5, 6, 7)	301	56.6	208/301	69	124/272	45.7
Fernmetastasen	38	53.5	9/38	23.6	2/35	5.7
Total	**702**	**54.8**	**558/702**	**79.5**	**406/639**	**63.6**

Gruppe 3 und 4 eine annähernd gleiche Erfolgsziffer zeigen, ist umso bemerkenswerter, als die Gruppe 3 das in unserem Material höchste Durchschnittsalter von 60.6 Jahren, während Gruppe 4 das niedrigste von 51.2 Jahren aufweist. Man sollte eher erwarten, dass bei älteren Frauen die konkurrierenden Todesursachen stärker ins Gewicht fallen würden. Es scheint demnach, dass Tumoren der Gruppe 3 von geringerer Malignität sind, indem sie längere Zeit lokal wuchern, bevor sie Metastasen setzen. Das Überschreiten der Schranke der axillären Lymphknoten verschlechtert bekanntlich wesentlich die Heilungsaussichten, auch bei technisch einwandfrei operablen Primärtumoren und Axillärmetastasen. Die Annahme einer geringeren Malignität der Tumoren der Gruppe 3, welche zum grössten Teil aus älteren Frauen zusammengesetzt ist (Verhältnis der Frauen unter 46 J. zu den älteren ist 1 : 10 gegenüber 1 : 2

1.

Carcinom, in 8 Stadien-Gruppen eingeteilt.

mindestens

3 J.		5 J.		7 J.		10 J.		15 J.		20 J.	
abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
43/49	87.8	28/37	75.6	21/28	75.0	12/15	80	4/5	80	0/1	0
65/79	82.1	45/67	67.1	33/53	62.3	14/30	46.6	2/9	22.2	0/4	0
16/24	66.6	6/15	40.0	3/10	30.0	2/2	100.0	0/1	0	0/0	0
83/151	55.0	51/127	40.2	34/104	32.7	15/74	20.2	2/24	8.3	2/12	16.6
50/136	36.8	21/108	19.5	12/90	13.3	6/71	8.5	0/33	0	0/18	0
8/38	21.0	2/33	6.0	0/26	0	0/17	0	0/10	0	0/6	0
7/79	8.9	1/70	1.4	1/64	1.6	1/54	1.8	0/38	0	0/16	0
0/30	0	0/25	0	0/22	0	0/17	0	0/11	0	0/10	0
272/586	**46.3**	**154/482**	**32**	**104/397**	**26.2**	**50/280**	**17.9**	**8/131**	**6.1**	**2/67**	**3.0**

2.

Carcinom, in Steinthal-Stadien eingeteilt.

mindestens

3 J.		5 J.		7 J.		10 J.		15 J.		20 J.	
abs.	%	abs.	%	abs.	%	abs.	%	abs.	%	abs.	%
43/49	87.8	28/37	75.6	21/28	75.0	12/15	80	4/5	80	0/1	0
164/254	64.5	102/209	48.7	70/167	42	31/106	29.2	4/34	11.8	2/16	12.5
65/253	25.7	24/211	11.4	13/180	7.2	7/142	4.9	0/81	0	0/40	0
0/30	0	0/22	0	0/22	0	0/17	0	0/11	0	0/10	0
272/586	**46.3**	**154/482**	**32**	**104/397**	**26.2**	**50/280**	**17.9**	**8/131**	**6.1**	**2/67**	**3.0**

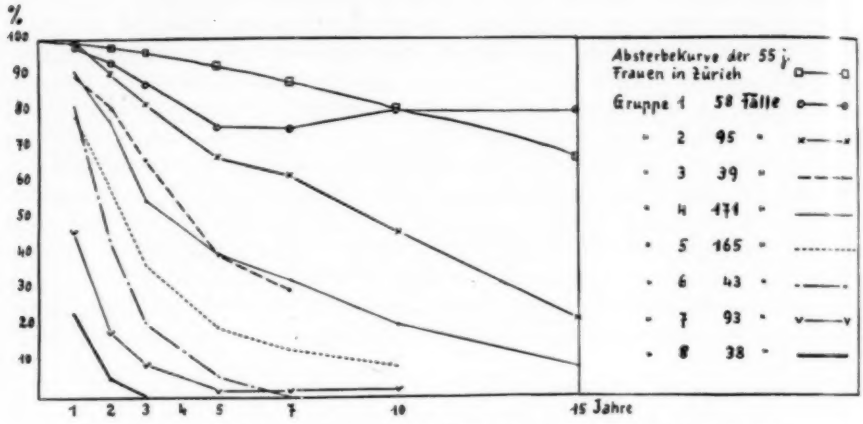

Abb. 1.[1] Überlebensdauer von 702 Fällen von Mammacarcinom in %, eingeteilt in 8 Gruppen.

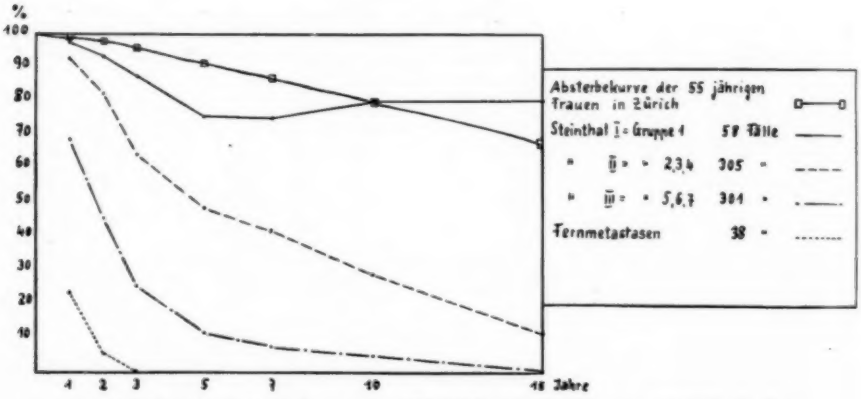

Abb. 2.[1] Überlebensdauer von 702 Fällen von Mammacarcinom in %, eingeteilt in Steinthal-Stadien.

[1] Die Kurven in Prozenten wurden bei den zahlreichen Gruppen bis zu einer Überlebensdauer von 15 Jahren eingezeichnet. Bei den Gruppen mit weniger Fällen wurden die Zahlen der Überlebenden so klein und die Streuung daher so gross, dass auf die Einzeichnung bis zu 15 Jahren zu Gunsten der Übersichtlichkeit verzichtet wurde. Die Absterbekurve der 55jährigen Frauen in Zürich kreuzt bei den 10 Jahre Überlebenden die Gruppe 1, was auf die starke Streeung infolge der kleinen Zahl zurückzuführen ist; ausserdem sind die Frauen unserer Gruppe 1 durchschnittlich um 3 Jahre jünger.

in Gruppe 4, s. Tab. 3), darf aber nicht zur Verallgemeinerung des Begriffes einer bessern Prognose mit fortschreitendem Alter verleiten. Erstens ist die Gruppe 3 sehr klein, sie enthält nur etwa 5 % unserer Fälle und ist 4mal kleiner als Gruppe 4, zweitens scheint die Prognose der jungen Frauen innerhalb dieser Gruppe nicht schlechter zu sein, denn eine von den nur 2 jungen Frauen hat 5 Jahre überlebt.

Um dem Problem der Prognose des Mamma-Carcinoms bei jungen Frauen im Vergleich zu älteren näher zu kommen, haben wir jede unserer 8 Gruppen in 2 Altersklassen eingeteilt und die Prozentansätze der Überlebenden nach 3 und 5 Jahren verglichen. Damit haben wir die Möglichkeit, Gleiches Gleichem gegenüberzustellen. Als Trennungsjahr beider Klassen haben wir das 45. Lebensjahr gewählt, um unter den jungen Frauen nur solche vor der Menopause zu erfassen. (Tabelle 3 und Abb. 3.)

Entgegen der verbreiteten Auffassung, dass das Mamma-Carcinom bei jungen Frauen bösartiger als bei älteren verläuft, einer Auffassung, die zum grossen Teil darauf beruhen mag, dass jeder rasch zum Tode führende Tumor bei einer jungen Frau dem Arzte einen tieferen Eindruck hinterlässt, als dies bei einer alten Frau der Fall ist, zeigt unsere Zusammenstellung, dass die jungen Frauen sogar in etwas besserem Prozentsatz 3 und 5 Jahre überleben als die älteren. Abgesehen von den 3 letzten Gruppen (6, 7 und 8), bei denen die Zahl der Überlebenden überhaupt sehr gering ist und einen Vergleich nicht gestattet, weist die Klasse der jüngeren um 8—25 % bessere Zahlen der 5 Jahre Überlebenden auf als die Klasse der älteren Frauen.

Bemerkenswert ist die verschiedene Alterszusammenstellung der einzelnen Stadiengruppen, die sich bereits aus der Errechnung des Durchschnittsalters (Tab. 1) vermuten lässt. Während das Verhältnis der jungen Frauen zu den älteren in den Stadien mit kleinen operablen Primärtumoren ohne Metastasen (Gruppe 1 und 2) sowie mit kleinen Primärtumoren mit axillären kleinen Metastasen (Gruppe 4) oder mit operablen supraklavikulären Metastasen (Gruppe 6) 1 : 2 resp. 1 : 3 ist, überwiegt bei den anderen Gruppen, besonders bei Gruppe 3 (grosse Primärtumoren ohne Metastasen) ganz entschieden die ältere Altersklasse (1 : 10 und 1 : 9). Aus dieser Tatsache lassen sich folgende Schlüsse ziehen:

1. Junge Frauen kommen wahrscheinlich etwas früher zur Behandlung (Gruppe 1 und 2 und 4). Ältere Frauen kommen verhältnismässig häufiger als junge in vollständig inoperablen Stadien erstmals in Behandlung (Gruppe 7).

2. Kleine, operable Primärtumoren scheinen bei jungen Frauen früher regionäre Metastasen zu setzen (Gruppe 4 und 6), was aber die

Tab. 3.

Überlebensdauer von 584 Fällen von Mamma-Carcinom (1919—1943) nach Stadium und Alter eingeteilt.

	Junge Frauen 132 Fälle (26—45 J.)				Ältere Frauen 453 Fälle (46—90 J.)				Verhältnis der jungen zur älteren Frauen
	3 J.		5 J.		3 J.		5 J.		
	abs.	%	abs.	%	abs.	%	abs.	%	
Gruppe 1.....	14/16	87.5	9/11	81.7	29/33	88	19/26	73	1:2
» 2.....	16/19	84.2	11/15	73.4	49/60	80.4	34/52	65.4	1:3
» 3.....	1/2	50	1/2	50	15/22	68.1	5/13	38.4	1:10
» 4.....	30/50	60	23/41	56	53/101	52.5	28/86	32.6	1:2
» 5.....	10/23	43.5	6/19	31.6	40/113	35.4	15/89	16.9	1:5
» 6.....	3/9	33.3	0/9	0	5/27	18.5	2/24	8.3	1:3
» 7.....	0/8	0	0/6	0	7/71	9.9	1/64	1.6	1:9
» 8.....	0/5	0	0/5	0	0/25	0	0/20	0	1:5
Total	**74/132**	**56.0**	**50/108**	**46.3**	**198/452**	**43.7**	**104/374**	**27.8**	**1:3½**

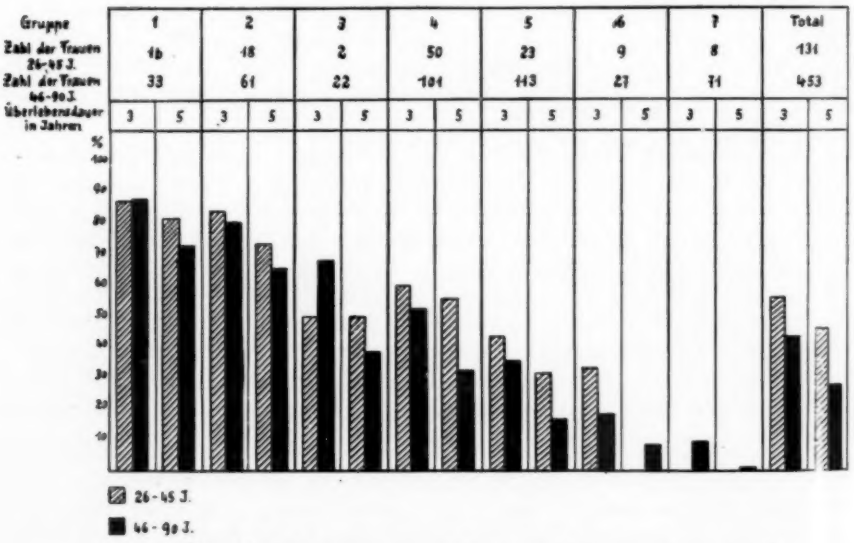

Abb. 3. Überlebensdauer von 584 Fällen von Mammacarcinom in %, eingeteilt nach Gruppen und Alter.

Prognose im Vergleich zu älteren Frauen im gleichen Stadium nicht verschlechtert.

3. Die wenig zahlreichen ausgedehnten Primärtumoren ohne Metastasen (Gruppe 3) kommen fast ausschliesslich bei älteren Frauen vor.

Schlussfolgerungen

Aus unseren statistischen Untersuchungen geht hervor:

1. Die Prognose des Mamma-Carcinoms wird hauptsächlich durch das Stadium des Primärtumors, die Lokalisation und Ausdehnung der Metastasen bestimmt. Das Stadium des Primärtumors tritt gegenüber dem Vorhandensein der regionären Metastasen an Bedeutung für die Prognose zurück, und zwar dank der kombinierten Therapie, welche erlaubt, einen inoperablen oder bedingt operablen Primärtumor durch die Vorbestrahlung in ein operables Stadium überzuführen, resp. durch Nachbestrahlung eventuelle Reste des Primärtumors zu vernichten. Dabei ist die Grösse und Zahl der regionären Metastasen weniger schwerwiegend, als die Tatsache, ob die erste (axilläre) oder die zweite (infraklavikuläre) Lymphknotenschranke durchbrochen wurde.

2. Es gibt eine kleine Anzahl von Mammacarcinomen (in unserem Material 5 %), welche besonders bei älteren Frauen vorkommen und spät metastasieren, trotz der starken lokalen Ausdehnung des Primärtumors. Sie weisen eine relativ günstige Prognose auf.

3. Bei gleichem Stadium des Tumors ist die Prognose unabhängig vom Lebensalter. Junge Frauen haben prinzipiell die gleiche Heilungschance wie alte Frauen bei gleichem Tumorstadium. Diese Tatsache bedarf noch einer Nachprüfung an grösserem Material. Vorläufig halten wir anhand unserer Erfahrungen die Indikation einer zusätzlichen Röntgensterilisation bei der Therapie der Mamma-Carcinome für nicht genügend begründet.

Die ausschlaggebende Bedeutung des Stadiums des Mamma-Carcinoms beim Beginn der Behandlung unterstreicht nochmals die Wichtigkeit der Grundsätze der Krebsbekämpfung: *Früherfassung*, *Früherkennung* und *Frühbehandlung*.

ZUSAMMENFASSUNG

Aus einem Material von 1,033 Malignomen der Brustdrüse, behandelt in der Radiotherapeutischen Klinik Zürich in den Jahren 1919—1945, wird an 702 genau klassifizierbaren Fällen von Mammacarcinomen eine statistische Analyse durchgeführt. Die 702 Fälle werden nach Schinz in genaue Stadien, welche sowohl den Primärtumor, als auch die Metastasen in Lokalisation und Ausdehnung berücksichtigen, klassifiziert, und in 8 Stadiengruppen eingeteilt. Die Prognose der einzelnen Stadiengruppen wird nach der

Zahl der Überlebenden beurteilt. Die Klassifizierung erlaubt für die verschiedenen Gruppen die Heilungschancen mit einer Genauigkeit von etwa 10—20 % vorauszubestimmen. Die Heilungsaussichten der jungen, im Vergleich zu älteren Frauen werden geprüft, indem jede Stadiengruppe in 2 Altersklassen getrennt, und die Prozentzahlen der Überlebenden beider Altersklassen einander gegenübergestellt wurden. Es ergibt sich, dass zwar eine kleine Gruppe von relativ günstiger verlaufenden Tumoren mit Vorliebe bei älteren Frauen vorkommt, dass aber innerhalb des gleichen Stadiums die jüngeren Frauen keine schlechteren Heilungsaussichten haben als die älteren.

SUMMARY

Collected from a material of 1033 malignant tumours of the mammary gland treated at the Radiotherapeutical Clinic in Zurich during the period 1919—1945, 702 cases permitting exact grading are studied in a statistical analysis. The 702 cases are classified according to SCHINZ in precise stages which take into account the primary tumour as well as the metastases, by considering both their localisation and extension. Subsequent adequate rating into 8 groups of different stages is carried out. An estimate of the prognosis of each group is made by relating it to the number of survivant patients. This classification permits to anticipate the chances of cure with an exactness of about 10—20 per cent. The prospects of recovery of younger women in comparison to those of the older patients are then examined by comparing the survival percentages of both age groups.

Thus may be stated that a small assemblage of tumours with relatively favourable evolution occur with predilection in older women. However, the prognosis in younger patients referable to the same stage is not worse than in older patients.

RÉSUMÉ

702 cas de carcinome mammaire chez lesquels une classification exate a été possible, sont étudiés dans une analyse statistique. Ces cas ressortent d'un matériel global de 1033 tumeurs malignes de la glande mammaire traités à la clinique radiothérapeutique de Zurich pendant les années de 1919 à 1945.

Les 702 cas sont classés selon SCHINZ en groupes nettement délimités, lesquels tiennent compte et de la tumeur primitive et des métastases, prenant en considération leur extension et leurs localisations. L'auteur en arrive ainsi à une répartition en 8 stades. Le pronostic inhérent à chacun de ces stades est apprécié d'après le nombre de survivants. Une telle distribution permettra d'anticiper dans chaque cas les chances de guérison possibles avec une exactitude d'env. 10 à 20 %. L'auteur examine ensuite les perspectives de guérison chez les jeunes femmes en comparaison avec celles des plus âgées. Cela faisant, il répartit selon l'âge les cas appartenant à un même stade en 2 sous-groupes et compare les nombres de survivants, calculés en pourcents, des 2 sous-groupes respectifs.

Il en résulte qu'un certain nombre de tumeurs à évolution relativement favorable se rencontrent avec prédilection chez des femmes plutôt âgées. Toutefois, les femmes plus jeunes appartenant au même stade n'ont pas de perspectives plus restreintes en vue d'une guérison que les malades plus âgées.

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RESULTS OF SURGERY AND RADIATION FOR CARCINOMA OF THE BREAST WITH AXILLARY METASTASIS[1]

by

K. W. Stenstrom and *O. J. Baggenstoss*

Is postoperative roentgen irradiation of value for carcinoma of the breast? This question has been raised repeatedly and the answers have varied. There seems to be only one method available to attempt an answer, and that is by means of statistics.

The difficulty with the statistical method is that so many variables enter in and it is always a question if one or more of these variables are weighted. The problem is to obtain normal samples.

The results from any therapy method differ tremendously with the stage of the disease. When a single freely movable mass in the breast is the only involvement of cancer found during a radical operation, surgery alone is very likely to result in a cure; and the patients in this group are, therefore, not suitable for a comparison. It is very doubtful that radiation would contribute anything to the survival in this group. When the disease is more extensive the results are less satisfactory, but comparisons are still difficult. A more specific criterion is needed and the one most usually adopted and the one probably most suitable and objective is involvement of axillary nodes as established histologically.

Another problem of special importance is the measure of results obtained. If the criterion »clinical cure» is used, then it depends upon how carefully the patient is examined (*e. g.*, roentgen films of chest and bones), and that is an unreliable factor. The cause of death is another term which may be used erroneously. Therefore, it seems advisable to use the uncorrected 5-year survival figure as a measurement of results, or still better, the survival curve. The assumptions then made are that

[1] Submitted for publication, May 7, 1947.

in different statistics, deaths from other causes than cancer of the breast would have similar distribution.

It is evident that the results will depend upon the methods of treatment and how skillfully they are carried out. This refers with equal consideration to the surgical and the radiological methods employed.

In a previous publication (2), the results obtained in all patients with carcinoma of the breast referred for roentgen therapy between the years 1926 and 1938 to the radiation therapy section at the University of Minnesota Hospitals have been discussed. At this time a study has been made of a selected group.

All patients who fulfilled the following criteria were included in this group:

(1) Had axillary node involvement at the time of operation proven by microscopic examination.

(2) Had no known distant metastases at the time of operation (lungs, liver, bones, etc.).

(3) Had postoperative roentgen ray therapy instituted within 32 days. The majority of patients were treated 10—14 days following operation.

(4) Had radical mastectomy performed at the University of Minnesota Hospitals. It may be mentioned that these patients were operated upon by a number of different surgeons, some of whom had limited experience.

Of all patients treated from January 1, 1927 to January 1, 1942, 110 fulfilled the aforementioned criteria. Records of those treated after 1941 were not studied as a 5-year survival could not be determined after that date.

Survival was computed from the date of operation. Untraced patients were considered to be dead as of the date of the last recorded information. Fortunately, it was possible to trace all but one patient at least 5 years or until death.

The youngest patient was 24 years and the oldest 79 years old. The ages according to decades are given in Table I. The median age was 51 and the average age 50.8 years. One male patient is included in this series.

Table I.

Age Incidence According to Decades

Age	Number of Patients
20—29	3
30—39	16
40—49	28
50—59	37
60—69	21
70—79	5

In our series of 110 cases, 45 or 41 % survived 5 years or longer. Of these patients, 37 or 34 % may be classified as »clinically cured» for 5 years, as 8 or 7 % were alive with recurrences. Table II presents the results in detail giving the number of patients treated each year and the percent surviving one, two, three years and so on up to 15 years following the operation.

The normal mortality rate for this average age (50) in five years is about 8 % and in ten years 19 %.

Table II.

Survival of Patients with Carcinoma of the Breast with Axillary Metastases Receiving Roentgen Therapy Following Radical Mastectomy.

Year	No. of cases	Number of Years														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1927	1	1	0													
1928	2	2	1	1	1	1	1	1	1	1	1	1	1	1	0	
1929	4	3	3	3	1	0										
1930	5	2	1	1	0											
1931	5	5	4	3	3	3	3	3	3	3	2	1	1	1	1	1
1932	5	4	3	2	1	1	1	1	1	1	1	1	1	1	1	
1933	12	8	7	6	5	5	4	4	4	4	2	2	1	1		
1934	11	10	8	6	5	5	5	4	4	3	3	2	1			
1935	8	7	5	5	5	5	4	4	3	3	3	2				
1936	2	2	1	1	1	0										
1937	3	3	3	2	2	2	2	2	2	1						
1938	7	7	6	4	3	3	3	2	1							
1939	16	16	12	11	11	9	9	7								
1940	16	14	10	9	8	7	7									
1941	13	10	10	8	5	4										
Total	*110*	*110*	*110*	*110*	*110*	*110*	*97*	*81*	*65*	*58*	*55*	*53*	*45*	*34*	*32*	*17*
Living		94	74	61	51	45	39	28	19	16	12	9	5	4	2	1
Percentage Living ...		85	67	55	46	41	40	35	29	27	22					

It has usually been considered that a radical mastectomy should be performed only when there seems to be a reasonable chance of removing all the cancer cells. Different criteria have been adopted by different surgeons. The only restrictions used here are: (1) The general condition of the patient prevents major surgery; (2) Distant metastases are definitely found; this includes unquestionably involved supraclavicular nodes; (3) Axillary nodes are very extensive and fixed; (4) Inflammatory carcinoma; (5) Carcinoma present after the fifth month of pregnancy.

No patients have been excluded from this series because of questionable operability, but serious consideration was given to the advisability

of including 10 of the cases. In 3 of the 10, the radiologist reported possible or probable lung metastases prior to operation. One of these patients lived 3 years, but the other two died within 3 months after the operation. The exact cause of death was not known in two of the cases, but the third one who lived only 3 months was known to have died of metastatic carcinoma. Five had local excision of the mass in the breast one to six weeks before they were referred to the University Hospitals for radical mastectomy for purpose of biopsy or under the impression it was benign. One had simple mastectomy about one month previous to the radical mastectomy; and in one patient, metastases, which could not be removed, were noticed under the clavicle at the time of operation.

None of these 10 patients survived five years. If they were excluded from the series, the 5-year survival would be 45 %.

Our group of those having local excision prior to radical mastectomy is too small to have any statistical significance, but HARRINGTON (4), in reporting a large series of carcinoma of the breast at the Mayo Clinic states:

»The poorest surgical results in carcinoma of the breast are obtained from secondary radical amputation after primary partial removal of the tumor. In approximately 10 % of the cases in which radical amputation has been performed at the Mayo Clinic, a minor operative procedure had been performed elsewhere one month or more prior to coming to the clinic. In this group, involvement of lymphatic structures had occurred in 74 % of cases as compared with 63 % of cases in which primary radical operation had been performed. The results of secondary radical amputation are correspondingly less satisfactory than those of primary radical amputation.«

ADAIR (1) condemns the procedure and also reports poorer results in such cases stating that:

. . . of the 283 cases classified as 'operable after local excision' there was a 5-year salvage of only 53 cases, representing 20 per cent. Had the patient been properly handled at the beginning she at least would have had a 51 per cent chance of 5-year cure.

Table III.

Comparative Statistics in Cases with Axiallary Metastases Proven by Histological Examination.

Author	Year	No. of Cases with Radical Mastectomy Only	% 5-year Survivals	No. of Cases with Radical Mastectomy Plus Post-op. Radiation Therapy	% 5-year Survivals
HARRINGTON (4)	1910—1935	732	24.3	2,011	29.4
HAAGENSEN & STOUT (3).	1915—1934[1]	154	28.2	143	26.0
JESSOP (6)	1923—1932	96	30.5		
Hooper & McGRAW (5)...	1918—1935	55	21.8	94	31.9
STENSTROM & BAGGENSTOSS	1927—1941			110	31.0

[1] Many of irradiated patients treated after 1923.

In Table III, statistics from some of the larger clinics are presented for comparison. These were particularly chosen from the literature because they reported their statistics as 5-year survivals[1] rather than as «clinical cures», and all their cases presented in the table had metastases to axillary nodes as proven by histological examination.

It has previously been shown that the clinical judgment of axillary metastases is a highly fallible procedure. In our series, 76 or 70 % had palpable axillary nodes and 33 or 30 % did not have palpable axillary nodes but all had involvement histologically.

In one patient there was no mention of an examination of the axilla. Of those who had palpable axillary nodes the 5-year survival rate was 43 %; and of those who did not, the survival rate was 36 %.

HAAGENSEN and STOUT (3) reported that in 325 cases in which axillary nodes were not palpable clinically, 143 or 44 % microscopically had axillary metastases. In 278 cases in which axillary nodes were thought to be involved by clinical examination 236 or 84.9 % had microscopic evidence of metastases an error of 15.1 %. HOOPER and MCGRAW (5) found that in 145 cases with palpable axillary nodes 111 or 76.5 % had demonstrable metastases (error 23.5 %). In 97 cases with no nodes palpable on clinical examination, metastases were later demonstrated in 38 or 39 %. SIMMONS, TAYLOR and WELCH (7) in their clinical appraisal of axillary involvement, noted that in 61 cases in which nodes were found on physical examination positive evidence of carcinoma was demonstrated in 53 or 87 % on microscopic examination; and in 79 cases in which no axillary nodes were felt, carcinoma was found on dissection of the axilla in 37 or 46 %.

Returning to the analysis of our own patients, it must be mentioned that radon seeds were used in 36 of the 110 cases and radium needles in one case (1,960 milligram hours). The amount of radon used varied from 1,267 to 4,360 millicurie hours, but in the great majority of cases approximately 4,000 millicurie hours was employed. The above 37 cases comprise the great majority of cases treated from 1931 to the middle of 1936, there being only two cases treated with radon after that. The radon seeds

[1] HAAGENSEN and STOUT in giving their five-year results of radical mastectomy in primary cases report 36.17 % alive, without recurrence 5 years after operation and 5.2 % alive with recurrence five years after operation or a total of 41.4 % alive at the end of five years. In reporting their cases with axillary node involvement, they report the results as 5-year clinical cures. We have taken the liberty of applying the proportion 36.2 : 41.4 to their 5-year clinical cures in order to express their results in this group as 5-year survivals. They report 24.7 % 5-year clinical cure for those with axillary node involvement treated by radical mastectomy only, and 31.5 % 5-year clinical cure for those who had postoperative prophylactic radiation plus radical mastectomy. The adjusted figures for the above two groups are 28.2 % and 36 % respectively. Though they are not exact, they should be close enough for comparison.

were implanted over the intercostal spaces and in the axilla, the exact location depending upon where the surgeon believed it would be of most benefit. Of these cases, 16 or 43 % survived 5 years or longer.

It is of interest to consider the location of the first discovered recurrence and this information is summarized in Table IV for 61 patients. In 20 of these patients the first recurrence was definitely in the irradiated area. This indicates that a heavier dose might have been more effective. We have since increased the dose to the anterior chest wall by adding tangential fields and have added one treatment of 300 roentgens to each of the supraclavicular and axillary fields. Whether or not this relatively small increase has been of any value may be determined in the future.

When distant metastases are the first indication of recurrence, it seems probable that they had occurred before the treatments were given. It, therefore, seems likely that only one-third of the patients in this group or one-fifth of all the patients included in this study might have received benefit from a heavier dose.

Table IV.

Recurrences in Sixty-one Patients

Site of First Recurrence	Number of Patients
Axilla	1
Supraclavicular	9
Anterior chest wall and scar	10
Node over sternum	1
Opposite breast	1
Opposite axilla	2
Generalized	13
Bone	15
Lungs	8
Liver	1

Irradiation sickness was not an infrequent occurrence, but we do not have any statistics regarding its frequency in our series. In no case was it severe enough to necessitate the cessation of therapy or reduce the total dose.

In three patients radiation lung fibrosis was reported by the radiologist after roentgen examination. In one of these patients, it was also reported that there were changes in the 2nd, 3rd, 4th and possibly 5th ribs on the right which might be accounted for by radiation necrosis. This same patient also had an ulcer at the apex of the scar in the right axilla which was attributed to radiation therapy. This ulcer was later excised and skin grafted with good results. None of these patients com-

pl ined of any distress referrable to radiation lung fibrosis. Two of these pa ients lived over 5 years (10 and 6 years) and one died 2 years after op ration.

One patient developed a severe dermatitis of the face, neck, anterior ch st wall, arms and hands which was diagnosed as roentgen dermatitis by the dermatologist although this patient gave a history of similar, les severe dermatitis previous to therapy.

For the period covered by this study (1927—1941 inclusively) only tw important changes occurred in the technique of postoperative roentgen the apy.

The majority of patients were treated from 10—14 days following the radical mastectomy, and the following physical factors were employed: 200 kvp., 30 ma., 0.5 mm. Cu and 1.0 mm. Al filter (H. V. L. 0.9 mm. Cu), focal skin distance 70 cm.

During the period 1927 to August, 1938, which included 56 patients, approximately 250 r (in air) was given every other day for four treatments (total about 1,000 r). This was directed to a field which included the anterior breast region, parasternal line medially, anterior supraclavicular cervical and axillary regions. The series was to be repeated in about 2 months, but some patients did not cooperate in this respect. After 1928, additional treatments were administered to the axilla and the supraclavicular region.

From August, 1938, through 1941, which included 54 cases, about 200 r (in air) was given every other day for six treatments (total 1,200 to 1,300 r) anteriorly to a field which included the above mentioned region. At the same time a treatment was directed posteriorly to the supraclavicular or axillary region, alternating these two fields with each anterior field. Three treatments of approximately 300 r (in air) each (total about 900 r) thus was administered to the supraclavicular and axillary regions in addition to what was given in the anterior field. A second series was not given under this plan.

Of the 56 patients treated during the period 1927—1938, twenty-one or 37.5 % survived 5 years or longer and of the 54 patients treated after the change in therapy 24 or 44.4 % survived 5 years or longer.

After 1941 the technique was again changed, and at present six treatments are administered to the large anterior field using 140 kvp., 15 m. a., 0.25 mm. Cu and 1.0 mm. Al filtration (H. V. L. 0.56 mm. Cu), focal skin distance 70 cm. 200 r (in air) is given at each treatment (total 1,200 r in air). The breast area also receives two tangential fields, from a lateral and medial direction, of 300 r (in air) to each employing 220 kvp., 15 m.a., 0.5 mm. Cu and 1.0 mm. Al filtration (H. V. L. 0.9 mm. Cu), focal skin distance 60 cm. The posterior axilla and supraclavicular areas are treated alternately with the above mentioned anterior and tangential fields with

300 r (in air) per treatment, total 1,200 r (in air) to each. The latter mentioned physical factors are used for these areas. Treatments are given every other day, the entire series extending over a period of about sixteen days. As yet no figures are available for patients treated with this technique.

Recurrences and metastases were usually treated as soon as they were discovered, but the technique used will not be discussed as it was selected to suit the individual case and varied considerably. Lung metastases were usually not treated. A few patients were given a sterilizing dose to the ovaries at the time of the first series of treatments and some of the others were sterilized when distant metastases occurred.

Discussion

Table III gives a collection of representative statistics, of the 5-year survival for carcinoma of the breast with axillary metastasis. It shows that radical mastectomy with modern technique as a rule produces less than 30 % 5-year survival. The addition of post-operative roentgen therapy has consistently increased the survival rate according to the figures in the table. The increase is not large, but the fact that it is consistent indicates definite advantage of post-operative irradiation.

The use of radon implants or radium needles in combination with the surgery for 37 patients complicates the statistics. Forty-three per cent of these patients survived five years or more and it seems probable that some benefit resulted from the radium therapy. Just as good results were, however, obtained with the improved roentgen technique when radium therapy was omitted and it, therefore, played a minor rôle.

The argument has been used that a full cancericidal roentgen dose cannot be delivered to a large field overlying the lung and that it, therefore, is useless to apply radiation. It must, however, be remembered that some carcinomas are destroyed with a much smaller dose than what usually is considered lethal and that only small foci of cancer cells are present after the surgery. The statistics also seem to bear this out. The method of therapy is, however, of great importance and it is doubtful that anybody as yet has discovered the most suitable volume and time distribution of the radiation. The fact that better results were obtained in our series after the method had been changed (from 37 to 44 %) may be an indication that it was improved and holds out hope for still better results in the future. It is, of course, possible that improved surgical methods should be given part of the credit.

SUMMARY

A survival study has been made off all patients with carcinoma of the breast who fulfilled the following criteria: A radical mastectomy had been performed at the University of Minnesota Hospitals. Post-operative roentgen therapy had been started within 32 days after the surgery. Satisfactory records were available to show that the pathologist had definitely found metastatic involvement of axillary nodes. No distant metastases were definitely known to be present at the time of surgery. The patients had been treated between January 1, 1927, and December 31, 1941.

A complete survival record up to December 31, 1946, of the 110 patients who fulfilled the criteria is summarized in a table. Forty-five patients (41 %) survived 5 years or more and twelve (22 %) lived 10 years or more after the operation. Representative statistics published by surgeons since 1936 have been selected to demonstrate results from radical mastectomy alone and with post-operative irradiation for patients with axillary metastasis. They show that post-operative roentgen therapy has consistently contributed to improved results.

ZUSAMMENFASSUNG

Es wurde eine Untersuchung der Lebensdauer vorgenommen an dem gesamten Material von Fällen von Brustkrebs, die folgende Bedingungen erfüllten: Eine radikale Mastektomie war in der Universitätsklinik in Minnesota vorgenommen worden. Innerhalb von 32 Tagen nach dem chirurgischen Eingriff war postoperative Röntgenbehandlung eingeleitet worden. Es lagen zuverlässige Angaben darüber vor, dass der Pathologe tatsächlich ein metastatisches Befallensein der Axillardrüsen gefunden hatte. Vorliegen von Fernmetastasen zur Zeit des Eingriffs war nicht bekannt. Die Kranken waren zwischen dem 1. Januar 1927 und dem 31. Dezember 1941 in Behandlung. In einer Tabelle wird eine vollständige Übersicht bis zum 31. Dez. 1946 gegeben der Lebensdauer sämtlicher 110 Kranken, die diese Bedingungen erfüllten. Fünfundvierzig Kranke (41 %) überlebten 5 Jahre oder länger, und zwölf (22 %) lebten 10 Jahre oder länger nach der Operation. Es wurden einschlägige, seit 1936 von Chirurgen veröffentlichte Statistiken gewählt, um die Ergebnisse radikaler Mastektomie allein sowie dieses Eingriffs mit postoperativer Bestrahlung bei Kranken mit Axillarmetastasen zu veranschaulichen. Sie zeigen, dass postoperative Röntgenbehandlung wesentlich zur Besserung der Ergebnisse beigetragen hat.

RÉSUMÉ

Étude de la survie de toutes les malades atteintes de carcinomes du sein qui remplissaient les conditions suivantes: une amputation radicale du sein avait été faite dans les hôpitaux de l'Université du Minnesota. Un traitement postopératoire par les Rayons Roentgen avait été mis en train dans les 32 jours après l'opération. On disposait d'observations satisfaisantes pour prouver que le pathologiste avait nettement trouvé un envahissement métastatique de ganglions axillaires. On n'avait pas constaté de façon certaine la présence de métastases à distance au moment de l'intervention chirurgicale. Les malades avaient été traitées entre le 1er janvier 1927 et le 31 décembre 1941. Un tableau condense jusqu'au 31 décembre 1946 les données complètes concernant la survie postopératoire des 110 malades qui répondaient à ces exigences. Quarante cinq patientes (41 %) étaient en vie 5 ans ou plus, douze (22 %) 10 ans ou davantage après l'intervention. Des statistiques, publiées par des chirurgiens depuis 1936, ont été choisies pour montrer les résultats de la seule amputation radicale du sein chez les malades atteintes

de métastases axillaires, et ceux qu'on obtient en y ajoutant l'irradiation. Elles font voir que la radiothérapie post-opératoire a contribué essentiellement à améliorer les résultats.

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MALIGNANT TERATOMAS AND SOME REMARKS ON THEIR RADIOSENSITIVITY[1]

by

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Malignant teratomas of the ovary are characterized by the presence of undifferentiated cellular elements of the three germinal layers, which exhibit unrestrained growth, form, and frequent mitoses. These tumors are extremely rare (8 in 1,100 ovarian tumors) GEIST (1), (2 cases in 1,300 ovarian tumors) KERMAUNER (2). It is doubtful whether more than 300 authentic cases have been reported up to the present time, CURTIS (3). These tumors usually occur in childhood or early youth, seldom after the menopause. They are usually unilateral and extremely malignant. FRANK (4), reports 88 % mortality within the first year after recognition of the tumor.

In spite of the rarity of these tumors, the gynecologist and radiotherapist are confronted with a serious therapeutic problem when the diagnosis is established. Is radical operation (bilateral salpingo-oophorectomy) and/or radiotherapy indicated when the disease is limited to one ovary? When the disease is extensive, there can be no objection to an attempt at radical extirpation and a program of radiation therapy. In the case of patients with disease limited to one ovary without extension, radical surgery or radiotherapy will naturally result in a sterile, eunuchoid individual.

A thorough review of the literature does not reveal a definite answer to this question; firstly, because of the small number of cases in any of the reported papers, and secondly because of a lack of analysis of the reported material. Most well known textbooks advise radical surgery. NOVAK (5), states that radiotherapy is of little value; BARZILAI (6), advises radical surgery and radiotherapy. Discussion of this therapeutic problem with many gynecologists of wide and diversified experience

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is equally divided; some advise radical surgery with or without radiotherapy in all cases, others advise only removal of the involved ovary without radiotherapy, on the ground that if other deposits are present no therapy is efficacious, and if disease is limited to one ovary, no other treatment is necessary, LADD and GROSS (7). Radiological literature and radiologists throw no light on this question other than that which can be inferred from the radiological response of the more numerous malignant teratomas of the testis, where the cytological features are similar to those of the ovarian tumors under discussion. It is well known that these malignant testicular teratomas are highly radio-resistent.

Since 1930 six malignant teratomas of the ovary have been admitted to the Mt. Sinai Hospital. The ages varied from 8 to 50 years; four were sixteen years of age or younger. The main symptom was abdominal enlargement over a period of several months to one year. The immediate symptom requiring hospitalization in all but one case, was sudden, severe lower abdominal pain, which was due in three cases to twisting and infarction of the tumor.

Case 1. M. B., Age 9. Admitted to Mt. Sinai Hospital, March 1930 for abdominal enlargement and lower abdominal pain. A mass arising from the pelvis and extending to umbilicus was found. At operation a tumor of right ovary was found, twisted and infarcted. There was no other gross evidence of disease at the time of laparotomy. Right oophorectomy was done; pathological report was malignant teratoma. Three series of fractionated roentgen therapy were directed to the pelvis, in April 1930, July 1930, and July 1931. The factors employed were 200 K. V. constant potential Filter H. V. L. 0.9 mm Cu; dose in mid pelvis at each series 960 »r». Patient never menstruated, developed into a tall, thin individual with sparse pubic and axillary hair and maldeveloped breasts. She was asymptomatic for 9 years. In 1939 patient returned complaining of pain and swelling in the right inguino-femoral region. A mass of firm lymph nodes was found measuring 6 × 8 cm in area with some deep fixation. Aspiration biopsy showed cells »highly suspicious of malignant neoplasm». Pelvic and general physical examination was otherwise negative. Roentgen therapy was directed to this area using 200 K. V. Thoraeus filter for a tumor dose of 4,000 »r» given in divided doses in a period of 30 days. There was no response whatever to this treatment and in several months there was increase in size of this deposit and palpable masses in the peritoneal cavity. Roentgen studies also revealed pulmonary deposits. Patient died in April 1940 with widespread disease. At no time was there palpable evidence of disease in the pelvis.

Case 2. L. L., Age 24. Admitted to Mt. Sinai Hospital August 1938. Gravida 1 para 0. Menses regular until age of 21 when they became irregular, occurring about every 2 months. Chief complaint was abdominal enlargement of one year duration. Physical examination was negative except for the abdominal mass which was the size of a full term gravidity. Laparotomy revealed a cystic tumor on a moderate pedicle. A left salpingo-oophorectomy was done. No other gross pathology was found. Microscopic diagnosis was malignant teratoma. Roentgen therapy was given following operation. Physical factors were 200 K. V., F. S. D. 80 cm filter H. V. L. 1.9 mm Cu, 4 portals 10 × 15 cm each. This was followed by intrauterine radium therapy, 3,380 mg hours. The estimated dose 3 cm from mid axis of the uterus at mid pelvis was 2,150 »r» from

th roentgen and 2,250 gamma »r» from the radium. Overall treatment time was 36 days. Pa ient was examined in March 1947 and no gross evidence of disease was found. Patient is menorrhoeic and asymptomatic $8^1/^2$ years after admission to hospital.

Case 3. A. H., Age 50. Admitted to Mt. Sinai Hospital November 1938 complaining of weakness, fever, generalized abdominal pain and distention. Masses were found extending to the umbilicus arising from the pelvis. Patient was operated upon and a large semi-cystic tumor of the left ovary was found infiltrating the broad ligament. Tumor nodules were also found in the omentum, mesentery and liver. Bilateral salpingo-oophorectomy and supravaginal hysterectomy was done. Patient died two weeks postoperative from pulmonary and abdominal complications. Diagnosis was malignant teratoma of ovary.

Case 4. E. C., Age 8 years. Admitted to Mt. Sinai Hospital July 1939 for acute pain in the left lower quadrant of several days duration. Physical examination was negative except for mass in left side of pelvis. At laparotomy a solid tumor was found measuring 8 cm in diameter on a twisted pedicle. A left salpingo-oophorectomy was done. Pathological diagnosis was malignant teratoma. The left half of the pelvis was irradiated with roentgen, tilting the two opposing beams laterally in order to minimize the effect on the right ovary. Physical factors 200 K. V. filter THORAEUS, F. S. D. 50 cm portals 8 × 10 cm. Dose to mid left pelvis was 2,100 »r» given in 26 datys. Patient was well in 1947. There was no gross evidence of disease and she was menstruating regularly since 1944.

Case 5. G. E., Age 16. Admitted to Mt. Sinai Hospital September 1942 complaining of enlargement of the abdomen for one year. Menses were regular every 28 days since the age of 13. Physical examination was negative except for pelvic mass which reached the umbilicus. Laparotomy revealed a large right ovarian tumor which had infiltrated the contiguous broad ligament and the posterior surface of the uterus. Bilateral salpingo-oophorectomy and supravaginal hysterectomy was done. Roentgen therapy followed operation; physical factors were 200 K. V. Filter H. V. L. 1.6 mm Cu. F. S. D. 80 cm. Dosage to mid pelvis was 2,160 »r». Abdominal and pelvic masses occurred shortly after operation and the patient died of widespread disease in March 1943, six months after admission to the hospital.

Case 6. H. L., Age 16. Admitted December 1944, complaining of lower abdominal pain and fever. Physical examination was negative except for a pelvic mass which reached the umbilicus. Upon laparotomy, bloody ascitic fluid was found and a tumor which had ruptured spontaneously. Bilateral salpingo-oophorectomy was done and the pathological report was malignant teratoma. No radiologic treatment was given, consent having been refused by the parents. Patient died 6 months later from intestinal obstruction due to recurrent tumor in the abdominal cavity.

Discussion

In analysing this small series of cases it seems clear that any malignant teratoma of the ovary which has spread beyond the primary focus will not survive, in spite of surgical removal and radiotherapy. The prognosis of these tumors even when limited grossly to one ovary is not uniformly good.

Case 1 was unusual in that she was asymptomatic for 9 years before metastatic disease became manifest and even at this time there may be no gross evidence in the pelvis. The growth restraining effect of the rather small amounts of post-operative roentgen therapy to the pelvis may have played some rôle. However, the metastatic deposits in the groin showed marked radio resistance to 4,000 »r» to the tumor bed.

Case 2 did receive radiotherapy in amounts that may be significant in destroying malignant teratomatous tissue. A combined dosage of over 4,000 »r» from roentgen and radium was given to mid pelvis. The use of the uterine cavity as a carrier for the radium is a useful method for increasing the dose to mid pelvis. This was first called to my attention in connection with the radiotherapy of ovarian tumors by Professor J. HEYMAN. This is probably the minimal dose lethal for malignant teratomas.[1]

Case 3 was hopeless from the time of admission. The occurrence at the age of 50 after onset of the menopause is most unusual and of interest.

Case 4. Treatment was directed to the side of the pelvis where the diseased ovary was removed. The tumor was on a rather long pedicle and it was decided to treat only the involved side with the hope of avoiding sterility and eunuchoidism. Patient received 2,100 »r» to the region of the left broad ligament. This amount of treatment is generally considered inadequate for the destruction of malignant teratomas and it is doubtful whether it played a rôle in the patient's survival.

Case 5. In spite of complete extirpation of ovaries, tubes and uterus and postoperative roentgen therapy, patient survived only six months. As stated above, a dose of 2,160 »r» to mid pelvis would not be expected to destroy this tumor. It is also likely that this patient had microscopic deposits throughout the abdomen at the time of operation because of the rapid evidence of generalized intra-abdominal disease shortly after laparotomy.

Case 6 had ruptured preoperatively. Bilateral salpingo-oophorectomy was done. Consent for radiotherapy was refused. Patient died within six months.

The rôle of radiotherapy supplementary to surgery is difficult to assay in so small a number of cases. It is fair to assume that these tumors are among the most radio resistant. Because of this, one may question the advisability of using radiotherapy routinely for malignant teratomas of the ovary where the lesion is limited to one ovary, especially when it occurs in a young individual who may be cured by unilateral oophor-

[1] Personal communication from Dr. MILTON FRIEDMAN who treated a large number of malignant teratomas of the testicle at the Walter Reed Hospital, Washington, D. C.

ect my. In older patients where sterility is not a factor, radiotherapy ma be employed to advantage, but the amount of irradiation to be eff tive will have to closely approach normal tissue tolerance.

SUMMARY

Malignant teratomas of the ovary are rare tumors occurring most frequently in you individuals. The mortality rate is very high during the first year of observation rega less of type of treatment. Radiotherapy may have some beneficial effect, but ther is not enough material to be statistically significant.

Because of the questional curative effect of radiotherapy, most authors advise that young patients with limited unilateral lesions should rely on surgery only for cure, in order to avoid sterility and eunuchoidism. Further experience with more patients and more effective radiotherapy may alter this point of view.

ZUSAMMENFASSUNG

Maligne Teratome des Ovariums sind seltene Geschwülste, die zumeist bei Jugendlichen vorkommen. Unabhängig von der Art der Behandlung ist die Sterblichkeit im ersten Beobachtungsjahre sehr hoch. Radiotherapie kann einen gewissen wohltuenden Einfluss haben, doch ist das Material noch zu gering, um statistisch signifikant zu sein. Wegen der fraglichen Heilwirkung der Radiotherapie rät die Mehrzahl der Autoren dazu, dass Jugendliche mit begrenzten einseitigen Affektionen nur chirurgische Behandlung bekommen, um Sterilität und Eunuchoidismus zu vermeiden. Weitere Erfahrungen mit einem grösseren Patientenmaterial und effektiverer Radiotherapie können diesen Standpunkt vielleicht verändern.

RÉSUMÉ

Les tératomes malins de l'ovaire sont des tumeurs rares, survenant le plus souvent chez des sujets jeunes. Le taux de la mortalité est très élevé pendant la première année d'observation, quel que soit le type de traitement. La radiothérapie peut avoir un certain effet favorable mais le matériel est encore insuffisant pour revêtir une importance statistique. A cause de la valeur curative douteuse de la radiothérapie, la plupart des auteurs conseillent, chez les malades jeunes à lésions limitées et unilatérales, de se fier à la seule chirurgie pour les guérir, afin d'éviter la stérilité et l'eunuchoïdisme. Les expériences à venir, faites sur un plus grand nombre de malade et avec une radiothérapie plus efficace modifieront peut-être ce point de vue.

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CARCINOMA OF THE OVARY DEVELOPING ON THE BASIS OF OVARIAN ENDOMETRIOSIS[1]

by

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The question whether ovarian endometriosis can be regarded as a preliminary stage of some cases of adenocarcinoma of the ovary, has not yet been sufficiently elucidated. The malignant degeneration of endometriosis seems in any case to be very rare and to demand different conditions favouring such a development. It seems possible to maintain, that a genesis of such an ovarian cancer cannot as yet be considered as definitely proved (AABERG etc.) (1). Under such circumstances it is appropriate to publish also such single cases, which seem to throw some additional light upon the said question. In spite of the relative frequency of the endometriosis itself, cases suitable for the above-mentioned purpose are exceedingly rare.

TEILUM (2) has recently published a case of ovarian adenocarcinoma, where a papillary tumour tissue, developed multicentrically, appeared on the inner wall of the endometrial ovarian cyst, where an invasive growth was observed in the cyst wall. In TEILUM's case there appeared transitory stages from »normal» epithelium to tumour epithelium, »identical» with cancer tissue of the uterus corpus. The state of things is such that the histologic picture of carcinoma of the corpus uteri undergoes considerable changes, depending on that stage of development the cancer happens to be in, and this being so, we can find in one and the same carcinoma of the corpus different histologically noticeable degrees of development. Nevertheless we can regard carcinoma of the corpus uteri — in spite of its different stages — as a relatively uniform phenomenon (3). We are confronted with a similar development in ovarian cancer.

At the Women's Clinic, University of Helsinki, where I am medical superintendent, we recently had a case which greatly reminds of that of TEILUM, and seems to testify in the same direction. The patient was a

[1] Submitted for publication, June 1, 1947.

la ourer's wife, aged 52, who was admitted to the hospital on Jan. 27th 1 47. The patient had been married for 30 years. There were 2 children, th first 29 and the second 27 years old. The deliveries had been normal, n abortions. Menstruation appeared at 16, was regular, the cycle was 2 days, time of duration 3 to 5 days. The monthly periods were accompa ied by pains and had stopped three years before the admission to ho pital, after having been irregular for 2 years before that. There were no special symptoms, only fatigue in the back during the last year, and to ards the close of the year some pains in the back and lower part of the abdomen, where the patient had noticed the formation of a protuberan e. There were no disorders in connection with stools and urination. The patient had lost somewhat in weight of late.

Sedimentation Rate 32/60. Hemoglobin 81. (Sahli) Wassermann —. Kahn —. Gonoreaction ± 0. The patient is of a pyknotic type as to her constitution. Gynecologic examination: the cervix is directed downwards to the back, lying more to the left. The body of the uterus not palpable separately. Above its supposed location there is a large tumour up to a finger's breadth above the navel, filling the whole of the minor pelvis and lying more to the right. The tumour is wedged in and adhering to the minor pelvis and cannot be dislodged upwards. It has a smooth surface, is fluctuating, not tender.

Thus the history is not any typical endometriosis history, nor does the gynecologic examination give any special indications in this direction. Clinical diagnosis: Cystadenoma pseudomucinosum.

On the 29th Jan. 1941. Supravaginal amputation of the uterus with bilateral oophorosalpingectomy and appendicectomy are performed. There is no fluid in the abdominal cavity. In the minor pelvis a tense tumour rises up to the level of the umbilicus, and the bladder is fixed on to its front surface to about halfway up to the navel. Behind the sigma is adhering to the tumour the whole way, and moreover a couple of loops of the small intestine are also affixed to the tumour. The uterus is not visible at all. To the right the coecum adheres to the tumour. The tumour is emptied by means of a sucker fixed to a trocar. Its contents are about two litres of a thick chocolate mass (typical endometrioma). The loops of the small intestine are first loosened. After that the sigma is detached beginning from the left, and during this process it is observed that the tumour extends intraligamentarily up to the side parametria. The ureter, the great blood-vessels and the psoas are laid bare. The bladder is displaced, and only after this the uterus becomes visible. Its blood-vessels are ligated and the round ligaments cut off. By going round the tumour from behind the right parametrium is reached, where the ureter strongly adheres to the tumour; it is detached. Down to the right there are single cysts containing serous liquid and affixed to the bottom of the culdesac.

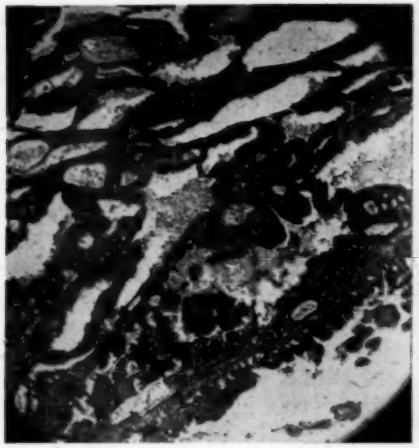

Fig. 1.

Fig. 2.

The rectum is still strongly adhering, by means of endometrial foci to the back surface of the cervix. The rough surfaces are peritonised. The adhering appendix is removed and the abdominal cavity is closed up. The patient leaves the hospital as convalescent on the 15th Febr. 1947. A roentgen treatment was begun previous to her departure, 32 × 300 r (THORÆUS).

Preparation: Uterus usual as to size and appearance. Adnexa indistinguishable macroscopically. The chocolate cyst looks otherwise as usual, except that there is on its back wall a separate rather soft tumour of a size of a small hen's egg, and some small similar nodes.

Several specimens are taken from the preparation for a histologic examination. The main results are given below.

Specimen I. From the large node on the wall of the endometrial cyst (chocolate cyst). Adenocarcinoma tissue, which is moderately anaplastic. In some places there appear growths of the »adenoma malignum» type. They are formed out of high cylindrical epithelium cells, which morphologically remind of the glandular epithelium cells of the corpus uteri. In some places there is a noticeable atypia. With stratified epithelium forming smaller solid areas. (Adenocarcinoma Fig. 1.)

Specimen II. From the wall of the chocolate cyst. It is composed of thick collagenic connective tissue, on the surface of which there is one row of cuboidal or columnal epithelium. Nothing malignant is to be noticed there. In one of the two specimens taken an inflamed connective tissue is seen, in the inner layer of which necrotic tissue is to be found.

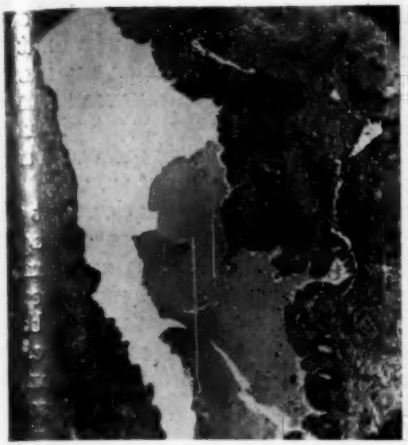

Fig. 3.

Fig. 4.

The epithelium is then absent for the most, in some places similar single-layered epithelium as above.

Specimen III. Taken from the supposed endometrial focus behind the cervix. No picture typical of an endometrial focus is to be found anymore, but only connective tissue bearing the marks of earlier hemorrhages, as well as large light so called pseudoxanthoma-cells.

Specimen IV. From the wall of the smaller cysts. Connective tissue is found there, which shows local lymphocyte infiltrations as well as similar pseudoxanthoma cells as in specimen III. Epithelium is entirely absent.

Specimen V. Taken from the lower part of the node. There is some thick collagenic connective tissue and here and there some small fasciculi consisting of smooth muscular tissue (probably originated from external organs affixed to the ovarian tumour and surrounding it). In this foundation tissue there are some typical endometrial ducts, showing cylindrical epithelium morphologically akin to the epithelium of the corpus endometrium, surrounded by a wide region of typical stroma tissue (cytogenous stroma tissue (Fig. 2)). In addition, numerous smaller regions are found in the preparation, which are composed of similar adenocarcinoma-tissue as in specimen I. In one place there is a larger oblong fissure-like canal, one end of which is edged by a high, cylindrical and only slightly atypical single-layered epithelium. In the other half there is instead a pronounced adenocarcinoma of characteristic papillary pattern. In the middle of this same canal a region can be observed, showing an

intermediate form between the cylindrical epithelium mentioned above and adenocarcinoma (Fig. 3). The specimen has in addition in a limited area of the thick connective tissue numerous small epithelium islets, whereof the greater part are solid, but some have a central small lumen formation. This epithelium has nothing in common with those pictured above, but it is morphologically similar to Walthard's cell indusions and the epithelium appearing in Brenner tumours (Fig. 4).

It seems evident on the basis of the histologic examination that we have to do with cancer developed from endometriosis. The patient aged 52 had already some time before passed the climacterium and consequently also the usual endometriosis age. Under these circumstances it must be supposed that the proper endometriosis growth has also been arrested. Instead the patient had just attained the best cancer age. It would therefore appear most natural, that the possibilities of cancer along with the age would also increase in such cases. Both macroscopically and microscopically my case shows a great similarity to that of TEILUM, where the patient was already 42 years old.

Conclusions

It seems that the question whether ovarian endometriosis can be regarded as a preliminary stage of some cases of adenocarcinoma of the ovary, is not yet definitely settled. The reported case provides perhaps some additional elucidation in this respect. The history of our case was not typical with regard to endometriosis. On the other hand, the large chocolate cyst reaching up to the level of the navel was a typical endometrioma. On the inner surface of the chocolate cyst a soft tumour of a size of a hen's egg was found (as well as some smaller protuberances), the histologic examination of which revealed a widely spread moderately anaplastic adenocarcinoma. The greater nodule also showed in some places adenoma-like regions, while the glandular epithelium reminded of that of the corpus uteri (Fig. 1). In the base of the tumour there were typical endometrial ducts and cytogenous stroma tissue (Fig. 2). At one end of a larger epithelial cavity a high columnar, single-layered epithelium was found, whereas there was an adenocarcinoma at the other end. In the middle of this same cavity there was an intermediate form between cylindrical epithelium and adenocarcinoma (Fig. 3). In addition, the same region had entirely different epithelium islets the epithelium of which was morphologically akin to Walthard's cell indusions and the epithelium of the Brenner-tumours (Fig. 4).

The case seems to prove that the epithelium of a typical endometriosis can undergo malignant degeneration, in the same manner as the glandular epithelium of the corpus uteri.

SUMMARY

A report is published of a histologically examined case elucidated by microphotographs, which seems to support the opinion that endometriosis can degenerate into carcinoma.

ZUSAMMENFASSUNG

Es wird ein Bericht veröffentlicht über einen histologisch untersuchten und mittels Mikrofotografien erklärten Fall, der die Ansicht zu unterstützen scheint, dass Endometriosis in Krebs degenerieren kann.

RÉSUMÉ

Rapport est fait sur un cas examiné histologiquement et élucidé par des microphotographies, qui semble confirmer l'opinion que l'endometriosis peut dégénérer en carcinome.

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CLINICAL AND PATHOLOGICAL SURVEY OF OVARIAN TUMOURS TREATED AT RADIUMHEMMET[1]

I. DYSGERMINOMAS

by

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A survey of the clinical features of the treatment used and of the prognosis and the results in ovarian tumours can be of value first when a large material collected over many years and treated according to uniform principles can be studied. For a survey of this type it is necessary to be able to use a classification of the tumour material which as much as possible is adapted to our modern knowledge both of the clinical and of the histogenetic and histological features of the tumours. Such a classification is especially difficult in the very intricate field of ovarian tumours, where as yet many problems as to histogenetic relations, structural variations and clinical behaviour are unsolved.

It is obviously necessary that in the collected tumour material the clinical histories and the follow up must be as complete as possible. Further, also the operative and biopsy specimens must be available for pathological studies to enable a histological classification of the material according to our present knowledge. A collection of a large material, where all these prerequisites are fulfilled, can only be assembled in institutions specializing in the treatment of tumours. Only in such clinics can for many years a complete record of the clinical histories and the available pathological material be assembled as well as a complete follow up be made.

Such principles have been followed in the organization of the clinical work and the follow up system of Radiumhemmet and in the assemblage and studies of the pathological material at the Radiopathological Institute.

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I it only if these principles are followed in all respects by tedious and u failing efforts during the daily routine work over many years, it is possible to collect a material of tumour cases large enough to make surveys o this type profitable. Professor HEYMAN has not only through his part in building up the organization of Radiumhemmet but also and even more by his never failing keen and admirable interest and efforts to keep up these principles during all his years as Head of the Gynecological department at Radiumhemmet made it possible to collect a material of inter alia ovarian tumours which is one of the largest and most thoroughly followed in all respects in the world. In these efforts he has had the ready help of clinicians and pathologists in most parts of Sweden, who during all these years have willingly contributed in the collection of the clinical histories and of the specimens for pathological investigations.

The material in question, collected until and including 1940 and in which five-year results can be ascertained, consists of about 700 cases. (Besides there are somewhat more than 250 cases where for different reasons specimens for pathological studies are not available or the existing pathological material is insufficient for accurate classification.)

In table I a preliminary division of the cases in different types is given.

Table I.

A.	Teratoid tumours.		
	1. So called gonocytomas.		
	a) Pure dysgerminomas	26	3.7 %
	b) Pure »mesonephromas»	3	0.4 »
	c) Combined teratoid tumours	4	0.6 »
	2. Other teratoid tumours, including dermoids	17	2.4 »
B.	Granulosa- and theca-cell tumours	53	7.5 »
C.	Papillary serous cystadenomas.		
	1. Benign or semimalignant	112	15.9 »
	2. Malignant	223	31.6 »
D.	Pseudomucinous cystadenomas.		
	1. Benign or semimalignant	32	4.5 »
	2. Malignant	58	8.2 »
E.	Solid and adenomatous carcinomas	53	7.5 »
F.	Cancer uteri et ovarii	83	11.7 »
G.	Metastatic carcinomas	25	3.5 »
H.	Unclassified carcinomas	12	1.7 »
I.	Fibromas and fibrosarcomas	6	0.8 »
		707	100.0 %

Radiumhemmet is a clinic principally for radiological treatment of tumours. For this reason, only those cases are referred and admitted to Radiumhemmet which might have benefit by such treatment. The

Table

Summary of the Clinical Records of

Case	Age at operation	Marriage. Pregnancies	Time and type of symptoms before operation	Findings	
				Type of operation. Size of tumour	Radicality
1. 1538/21 H. V.	31	Married III	3 months. Noticed tumour	July 21: salp.-oophorect. bil.+hysterectomy. Man's head	Complete. Ruptured
2. 639/22 K. A.	27	Married III	Noticed at delivery. Oper. 17 days thereafter	July 22: oophorect. dx> Man's head	Comp.
3. 141/23 S. E. B.	28	Married. Abort. at 41 years	1 month. Increasing abdomen	Jan. 23: salp.-oophorect. sin. Man's fist	Comp.
4. 3801/27 E. M.	23	Unmarried 0	1 month. Noticed tumour	1) April 23: salp.-oophorect. bil. 2) May 23: ext. of met. in operat. scar. > Walnut-sized	Incomp. Rupt.?
5. 3247/28 E. O.	31	Married I	3—4 months. Noticed tumour	Jan. 27: salp.-oophorect. bil.+amp. uteri supravagin. Size not stated	Comp.
6. 4620/28 N. E.	23	Married I (+ II)	4 months. (Noticed at delivery. Operat. 4 months later)	April 28: salp.-oophorect. dx. Large »as 7 months gravidity»	Comp.
7. 5694/28 H. M. J.	41	Married 0	2 years. Lost 17 kg. Noticed tumour	Jan. 28: salp.-oophorect. bil. +hysterectomy. Before rtg. < man's head. At operat. child's head	Incomp.
8. 1682/29 M. E. L.	16	Unmarried 0	2—3 months. Lost weight. Noticed tumour	Jan. 29: salp.-oophorect. dx. Man's head	Incomp. Rupt.
9. 4189/30 E. J. E.	24	Unmarried 0	?	May 30: salp.-oophorect. dx. Man's fist	Comp.
10. 318/32 H. V. S.	24	Married 0	?	May 31: ovariotomia dx. Man's head	Comp.
11. 2528/32 M. T.	17	Unmarried 0	2—3 months. Noticed tumour	Febr. 32: salp.-oophorect. dx. Grape-fruit-size	Comp.
12. 5667/33 K. K. J.	23	Unmarried 0	No symptoms. (Examined for health certificate)	July 33: salp.-oophorect. sin. Man's head	Comp.
13. 3887/34 A. M. L.	26	Married 0	? Abdominal pain	March 34: salp.-oophorect. bil. + hysterectomy. Child's head	Comp.

I

th 37 Cases of Radiumhemmet.

o	eration		Radiological treatment	Follow up
de	Other ovary	Clinical malignancy		
.	0.	0.	August 21: postop. rtg.+ ra. in the vagina	Symptomfree 7 years. (Then lost track of. Emigrated U. S. A.)
.	0.	4 lit. ascites	Sept. 22: ra. intrauterine	Clinic. pelvic recurr. at beginning of ra-treatment. Symptomfree 24 years
.	Cystic	0.	Jan. 23: postop. ra. and rtg.	Symptomfree 24 years. Abortion at 41 years
Bilateral		Periton. metast.	May 23: postop. rtg. and rtg. against recurrences	Symptomfree nearly 4 years. Then rec. and dead 5 years after operation
.	Cystic.	Some adhesions	Febr. 28: heavy postop. rtg. treatment	Clinic. pelvic recurr. 1 year after operation (goose-egg-sized, left-sided lump.). Disappeared p. rtg. Thereafter symptomfree 19½ years. (Has had lupus vulg. and lymphoma tbc.)
R.	0.	Thick omental adhesions.	Sept. 28: rtg. against recurrences	Clinic. pelvic recurr. 4 months after operation. (Large epigastr. tumours+inguinal metast.) Disappeared p. rtg. Symptomfree 18 years. (Two normal deliveries 9 and 10 years after operation)
R.	0.	Beg. cachex. Firmly fixed. Diffic. to remove	Dec. 28: prae- and Febr. 29. postop. rtg.	Symptomfree 3 years. Then mediastinal metastases and dead nearly 4 years after operation
R.	0.	Oment. and mesenteric lgl. metastases	(Postop. rtg.) Very small doses	Death from tumour 1½ month after operation
R.	0.	0.	June 30: postoperative rtg.	Symptomfree 16 years
R.	0.	0.	June 31: postop. rtg. (only right side) + ra intrauterine and in vagina	6 months after operation. clinic. recurr. (Orange sized lump in right groin). Symptomfree 15 years
R.	0.	0.	March 32: postoperative rtg.	Symptomfree 7½ years. (Since then not followed)
L.	0.	0.	August 33: postoperat. ra+ rtg.	Symptomfree 13½ years
R.	0.	Adherent to uterus	May 34: postoperat. rtg.+ ra.	Symptomfree 12½ years

Table

Case	Age at operation	Marriage. Pregnancies	Time and type of symptoms before operation	Findings at	
				Type of operation. Size of tumour	Radicality
14. 6156/34 A. T. J.	32	Married I	10 months. Rapidly enlarg. abdomen. Lost weight	August 34: oophorect. dx. Man's head	Comp.
15. 2555/35 K. T. F.	42	Married III	1/2 year. Enlarging abdomen. Lost weight	Febr. 35: Extirp. partial. tumour ov. dx. Child's head	Incomp. Rupt.
16. 6555/35 A. L. K.	33	Unmarried 0	3 months. Noticed tum. Lost weight	August 35: salp.-oophorect. dx. et oophorect. partial. sin. Right: Man's head. Left: hen's egg	Incomp.
17. 5621/37 I. M. E.	10	Unmarried 0	?	Febr. 37: oophorect. dx. Man's fist	Comp.
18. Västerås 145/37 L. V. L.	27	Unmarried 0	1 1/2 months. Pains. Enlarging abdomen. Lost weight	August 37: oophorect. sin. Weight 4 1/2 kg.	Comp.
19. 9294/38 V. N. J.	20	Unmarried 0	2—4 months. Pains. Noticed tumour	Dec. 37: salp.-oophorect. dx. Man's head	Comp.
20. 8336/38 A. D. E.	21	Unmarried 0	3/4 year. Noticed enlarging tumour	August 38: salp.-oophorect. dx. Man's head	Comp.
21. 597/39 G. S.	18 1/2	Unmarried 0	About 1 month. Pains	1) Dec. 38: salp.-oophorect. bil.+amput. uteri supravagin. Res. omenti 2) June 39: extirp. of periton. metast. Man's head	Incomp.
22. 7605/39 E. L. L.	19	Unmarried 0	Some months. Lost weight. Acute fever	1) June 39: salp.-oophorect. dx. 2) July 40: salp.-oophorect. sin. 1) Weight 4 kg. 2) Child's head	1) Comp. 2) Comp.
23. 8897/39 M. P.	31	Married 0 (II)	1/2 year. Noticed enlarging tumour	August 39: salp.-oophorect. dx. 18×13×13 cm.	Comp.
24. 2175/40 M. I. L.	14 1/2	Unmarried 0	? Acute heavy pains	Jan. 40: salp.-oophorect. dx. Grape-fruit-sized	Comp.? Rupt.
25. 11475/40 M. K. E. A.	29	Unmarried. Later married 0 (I)	? Diagnozed at investig. for polyarthr.	Nov. 40: salp.-oophorect. dx. More than child's head	Comp.

F (Cont.)

Operation			Radiological treatment	Follow up
Side	Other ovary	Clinical malignancy		
R.	0.	0.	Sept. 34: postoperat. ra.+ rtg.	Symptomfree 8 years. (Then dead through traffic accident)
Bilateral		Peritoneal implant. metastas.	March 35: postoperat. ra.+ rtg.	At first symptomfree 8 months. Then sudden death. Autopsy: liver metastases. Locally no tumour
Bilateral		0.	Sept. 35: postoperat. ra.+ rtg.	At first symptomfree 4 years. Then rather sudden death from liver metastases
R.	0.	Fresh omental adhesions	Sept. 37: rtg. against recurr. upper abdom.	After operat. symptomfree $2^1/_2$ years. Then large tum. place of liver, plum-sized splenic region, fist-sized in pelv. region. All disappeared after rtg. Then symptomfree $3^1/_2$ years. Then clinic. recurr. left pelvic region. Again rtg. Since then symptomfree. (Together 9 years.)
L.	0.	0.	(Prae- and postoperat. rtg.) Very small doses	Dead from retroperitoneal metastases after 4 months
R.	0.	0.	Dec. 37: postoperat. rtg.	Symptomfree $8^1/_2$ years
R.	0.	Thin adhesions	Oct. 38: postoperat. rtg.	$1^1/_2$ month after operat. lgl. metast. disappeared after rtg. Dead from lung metastases 9 months after operation
R.	0.	Oment. adhes.+ +metast. omenti	Jan. 39: postoperat. rtg.	Recurr. r. hypochondr.+metastases in lgl. and oment. After rtg. nearly all disappeared. Dead from peritoneal metastases 8 months after 1st operation
R. — L.	0.	At both operat. ascites. Recurr. l. side torquated	July 39: postop. rtg. r. side. After 2nd operat. both sides	At first symptomfree 1 year. Then recurr. l. ovary. After 2nd operat. symptomfree. Together $7^1/_2$ years
R.	0.	0.	Sept. 39: postop. rtg. only r. side	Symptomfree 7 years. Pregnancies 1940 and 1943. First foetus stillborn, malformed
R.	0.	Firm adhes. in Douglas	Febr. 40: postop. rtg.	1 month after operat. recurr. l. side. Later metast. l. arm. disappeared after rtg. Death after 6 months
R.	Cystic	0.	Dec. 40: postop. rtg.	Symptomfree 6 years. Normal pregnancy 1943. (Child normal.)

Table

Case	Age at operation	Marriage. Pregnancies	Time and type of symptoms before operation	Findings at	
				Type of operation. Size of tumour	Radicality
26. 11584/40 E. M. F.	39	Married 1	1 month. Pains. Lost weight	Dec. 40: salp.-oophorect. dx.+amput. uteri supravagin. (myoma). Grapefruit-sized	Comp.
27. 9080/41 C. A. Br.	23	Unmarried 0	? Blood coughing 1 year. Discovered at control examination	June 41: salp.-oophorect. sin.	Incomp.
28. 12164/42 B. H. N.	27	Unmarried 0	1 year. Pains. Enlarging abdomen. Noticed tumour. Lost weight	August 42: salp.-oophorect. bil. < Child's head	Incomp.
29. 9801/43 I. G. K. H.	31	Married 0	1 month. Enlarging abdomen. Lost weight	April 43: salp.-oophorect. bil. Grape-fruit-sized	Incomp.
30. 4136/44 M.-B. H.	22½	Unmarried 0 (Abort provoc.)	A few months. Tired. Acute pains	1) Jan. 44: salp.-oophorect. sin. Ovariotomia dx. 2) Aug. 44: abortus provoc. 3) Oct. 44: oophorect. dx. 1) Man's fist 3) Child's fist	Comp.? Rupt. Incomp. Rupt.
31. 8842/44 N. N.	24	Unmarried 0	? Acute abdominal pains	April 44: salp.-oophorect. bil. Child's head	Comp. Rupt.
32. 217/45 G. I. S.	18½	Unmarried 0	? Acute abdominal pains	Febr. 45: salp.-oophorect. dx. Man's fist	Comp.
33. 813/45 A. L. V.	15¾	Unmarried 0	2—3 weeks. Difficulties at urination	Oct. 45: salp.-oophorect. sin. Man's fist	Comp.
34. 163/46 E. N.	26¾	Unmarried 0	3 months. Enlarging abdomen. Noticed tumour	Febr. 46: salp.-oophorect. bil. Left: child's head. Right: biljard ball	Comp.
35. 965/46 E. I. V.	18	Unmarried 0	7 months. Misinterpreted as gravidity. Zondek pos. Pleural exsudate dx.	Dec. 46: salp.-oophorect. bil. More than man's head	Comp. Rupt.
36. 999/46 A. M. Y.	21½	Married 0	? No symptoms (operated for uterus subseptus)	Nov. 46: salp.-oophorect. dx. Resectio ov. sin. Double man's fist	Comp.
37. 70/47 K. M. K. B.	24	Unmarried 0	About 1 year. Pleural exsudate dx.	Jan. 47: salp.-oophorect. dx. Child's head	Comp.

II (Cont.)

Operation			Radiological treatment	Follow up
Side	Other ovary	Clinical malignancy		
R.	0.	Infiltrat. of r. tube	Dec. 40: postop. rtg.	Symptomfree 5 years
Sin.	0.	Firm adhesions. Partly lying retroperitoneally. Some small peritoneal metastases	July 41: postoperative rtg. 3 years later rtg. against mediastinal metastases	At beginning of rtg-treatment walnut-sized local recurrence. Disappeared. Symptomfree 3 years. Then rtgenological lgl-metastases in mediastinum. Disappeared after rtg-treatment. Then symptomfree 1 year. (Together $5^1/_2$ years.)
R.	Metastas L.	Bloody ascites. Torqu. Large metast. f. Douglas. periton., around vasa femoral. etc.	Sept. 42: postop. rtg.	At beginning of rtg. treatment large pelvic tumours palpable. Disappeared thereafter. Symptomfree 3 months after operation. Later recurr. and death $6^1/_2$ months after operat. Autopsy: periton. metastases
R.	0.	Infiltrat. in colon pelvinum	May 43: postop. rtg.+ra.	At beginning of rtg. treatment plum-sized pelvic recurr. Disappeared after rtg. treatment. Then symptomfree. Together $3^3/_4$ years
L.	Cystic Metastasis	1) Fresh blood in abdomen 3) Metastas. iliac lgl. and in f. Douglas.	Febr. 44: postoperat. rtg. + ra.	6 months after operation pregnancy revealed. 2 months later abortus provocat. 3rd operat. 9 months after 1st. Then symptomfree 8 months. Death from distant metastases (among others left scapula) $1^3/_4$ year after 1st operation
L.	0.	Much fresh blood in abdomen	April 44: postoperat. rtg.+ ra.	Symptomfree $2^1/_2$ years
R.	0.	0.	March 45: postoperat. rtg.	Symptomfree $1^3/_4$ years
L.	0.	0.	Nov. 45: postoperat. rtg.	Symptomfree 1 year
Bilateral		Right tum. adherent to colon pelvin.	March 46: postop. rtg.+ra.	Symptomfree 10 months
R.	0.	Thin adhesions. Tumour-pieces free in abdomen	Dec. 46: prae- and postoperat. rtg.	After praeoperat. rtg. tumour markedly diminished. Symptomfree
R.	0.	Firm adhesions in Douglas. Metastasis in right parametrium	Dec. 46: postoperat. rtg. (small dose. Patient disrupted treatment)	Symptomfree
R.	0.	0.	Jan. 47: postoperat. rtg. (only right side)	Symptomfree

material collected there must, thus, be of a specially selected type and not representative of the materials found in clinics for general surgical treatment.

This paper gives a survey of the group of cases belonging to the tumour type, mentioned first in table I, that is the dysgerminomas. Only those cases are included here which in all respects and exclusively show histological structures typical for this special rather rare type of ovarian tumour. Thus, tumour cases in which dysgerminomatous structures are combined with others for example adenopapilliferous, chorionepitheliomatous or pure teratoid structural elements are not included. As can be seen in table I the material collected until and inclusive of 1940 contains 26 pure dysgerminomas. In the following years 11 further cases of pure dysgerminomas have been treated at Radiumhemmet which cases are also dealt with in this survey. The whole material of pure dysgerminomas, surveyed here, consists, thus, of 37 cases. In 27 of these cases the five-year results can be studied.

This special, rare type of ovarian tumour has been the subject of great interest and vivid discussions as to its histogenesis and histological and clinical characteristics. Histologically it has a similar structure as the seminoma occurring in the testis, which has been long recognised. First in 1911 CHENOT pointed out its occurrence in the ovary and since then it has been given a variety of names among which may be mentioned ovarian seminoma, embryonal carcinoma with lymphoid stroma, »tumeur de l'ovaire des fillettes», carcinoma ovarii puellarum, sex cell carcinoma, »Grosszelliges solides Carcinom der Jugendlichen und der Scheinzwitter» and large round cell sarcoma. The now generally adopted term, dysgerminoma, was proposed by R. MEYER. It clearly denotes the imperfect germinal character of the tumour, which is made up of cellular elements of embryonal type indistinguishable from the sexually undifferentiated mesenchymal cells of the early gonad.

These special features have given rise to the hypothesis that the cells of these tumours apparently are derived from cells of the primitive gonad at a very early period and before male or female sex characters have been imparted to them. They are, thus, supposed to arise from germinal cells that are neither male nor female in type, but are neuter or dysgerminal (R. MEYER). This assumption is demanded by the absence of sex properties and by the occurrence of similar tumours in the testis. However, on account of the fact that some dysgerminomas associated with teratoma and even with chorioma have been found, many especially american authors, among others EWING, are of the opinion that the tumours represent one-sided developments of a teratoma. In recent years further support for this latter opinion has come forth through the works of TEILUM. In comparative studies of testicular and ovarian tumours he has

given convincing evidence for the opinion that the dysgerminomas form a first group in a whole series of tumour types, by him called the gonocytoma series, in which the other related types are partly an adenopapilliferous type of tumour, earlier sorted out and described by SCHILLER under the name of mesonephroma, and partly ovarian choriomas. The ovarian tumour material of Radiumhemmet gives a strong support to the just mentioned theory of teratoid origin as well as to this classification, recently advanced by TEILUM, as it contains no less than 7 tumours in which are found different combinations of both adenopapilliferous, choriomatous, teratoid and dysgerminomatous structures. (See Table I.)

In this survey, however, only those cases are included, whose tumours exclusively show pure dysgerminomatous structures. It is evident that this restriction is artificial when considered in the light of our modern knowledge of the histogenesis of these tumours and their close relation to the tumour types just mentioned. On the other hand, through this restriction the survey of the clinical features, the prognosis and the results of treatment concern a material of an as much as possible clearcut and pure type of tumour. The restriction is further warranted, because the related tumour types, judging from the cases described in the literature and from those in the material of Radiumhemmet, seem to be clinically more malignant and less radiosensitive than the dysgerminomas. As such a rigid restriction has not been followed in the earlier published cases of dysgerminomas, it is obvious that the comparisons made in the following with cases assembled from the literature are affected with uncertainty.

The literature regarding dysgerminomas is now rather extensive, but contains, as it is usual with rare and special tumours, mostly casuistic descriptions of only one or a few cases. Larger collections have been published by especially NOVAK and GRAY, 1938, SEEGAR, 1938, and FÖDERL, 1938. Of these authors SEEGAR collected 79 cases from the literature and 19 own cases besides 23 cases earlier described by R. MEYER with tumours in hermaphrodites and pseudohermaphrodites. In the present paper further 113 cases have been assembled from the literature since the paper of SEEGAR.

The material presented here (37 cases, for 27 of which five-year results are available) is the largest thoroughly followed that has hitherto been published from one clinic. It may in this connection be mentioned that among all the 192 cases assembled from the literature, there are only 80 for which the five-year results are given. Furthermore, nearly all the cases of Radiumhemmet have obtained adequate postoperative radiological treatment. For this reason, especially the prognosis as well as the results of and other questions in connection with the radiological treatment can be more thoroughly studied in this material than in those earlier published.

On the other hand, as regards the macro- and microscopical characteristics of these tumours nothing new has come forth in this tumour material.

The incidence of pure dysgerminomas in the whole material of ovarian tumours at Radiumhemmet is 3.7 %. (If only the histologically clearly malignant tumours are counted the incidence is 5.0 %.) However, as has already been pointed out, this material is only representative for a clinic specializing in radiological treatment of tumours. In the literature KLAFTEN (1934) from a series of 188 malignant ovarian tumours estimated the incidence at about 3 %, FÖDERL (1938) at 4 % (from 319 cases) and SAILER (1940) at about 6 % (from 80 cases). In the material of SJÖVALL (1943) (from the Pathological Institute in Lund, Sweden) of 678 ovarian tumours in general there was 0.7 % dysgerminomas.

The clinical records of the 37 cases of pure dysgerminomas surveyed here are summarised in Table II. The case numbers given in brackets in the following refer to the cases in this table.

Clinical Features

The local symptomatology of dysgerminomas is generally not distinctive and corresponds mostly to that of other solid ovarian tumours. In early cases the tumour frequently gives no symptoms and it may be discovered accidentally. This has occurred in five cases in this series (2, 6, 12, 25 and 36, the first two of these cases discovered at delivery). In general, however, there are some clinical features which aid in arriving at a preoperative diagnosis. These are especially the duration of symptoms and the age and sometimes also the clinical development of the patient. In this tumour series the leading symptoms have been abdominal swelling with noticing of a tumour mass in the lower abdomen and pains as well as loss of weight. The duration of symptoms has in this series, as in the earlier described cases, mostly been very short, suggesting a rapid tumour growth. Thus, three cases (24, 31 and 32) have acutely fallen ill, whereas for most of the others the symptoms have been noticed less than 4 months (17 of 25 cases). In only one case (7) the duration was about 2 years and in 7 cases it was from 6 months to 1 year.

R. MEYER (1925) and later many other authors have laid stress upon the frequent occurrence of dysgerminoma with pseudohermaphroditism, hypogenitalism and other forms of sexual maldevelopment. The coexistence of such abnormalities, thus, may suggest the right diagnosis. In this material, however, only two cases (8 and 36) showed such maldevelopments (nr. 8 infantile uterus and 36 uterus subseptus) and in 129 cases (of 187), collected from the literature, the tumour occurred in an otherwise normal person. At the time of operation 14 of the cases in this series were married and of these 7 had had children. After the treatment

ne of them (6) and 4 of the others (3, 23, 25 and 30) have been pregnant. (See also later.)

The dysgerminoma predominantly affects young individuals under 30 years of age (about 81 %); in 28 of the cases in this series the tumour occurred while the patient was under 30. (See Table III.)

Table III.

Age incidence	0 to 9	10 to 19	20 to 29	30 to 39	40+	Total Cases
Cases (Radiumhemmet)	0	9	19	7	2	37
Cases (Literature)	6	86	66	24	10	192
	2.6 %	41.5 %	37.1 %	13.5 %	5.3 %	

Another proof of the rapid growth of these tumours is that in spite of the usually short duration of symptoms, the tumours mostly attain large sizes. Tumours of the size of a man's fist or a man's head are rather common. In this series no less than 31 of the cases had tumours of such sizes. The smallest was walnut-sized (4).

The malignancy of the dysgerminomas appears partly through infiltration per continuitatem of the surrounding tissues (see fig. 4), partly by giving rise to metastases. The infiltration occurs especially along the intraligamentary lymphways and further in the subperitoneal spaces. The free capsule is only rarely broken through, but large tumours may rupture and in this way produce peritoneal implantation metastases (FAUVET, FÖDERL). Rupture may occur either spontaneously or at operation. It is, judging from this material, of rather serious consequences. It had occurred before the operation in six of the cases treated more than 2½ years ago (4, 8, 15, 24, 30 and 31). Five of them have died, although in two (24 and 30) the operation was considered radical. The three other cases (4, 8 and 15) had peritoneal implantation metastases at the operation. (The living case, 31, was operated only 2½ years ago.)

These tumours predominantly metastasize along the lymphatics, firstly to the retroperitoneal lymph nodes along the big abdominal vessels, later to the mediastinal lymph nodes. From there they may disseminate through the thoracic duct to the supraclavicular region (HOCHE, DWORZAK, FÖDERL and SJÖVALL.) Metastases to other organs do also occur. (Lung-, liver-, pancreas-, spleen-, kidney- and bone-metastases are described by among others NOVAK and GRAY, SEEGAR, HOHAGE.) Haematogenic dissemination may occur, but is rare. (Cases described by among others FÖDERL and SJÖVALL.) In this series of cases two (24 and 30) have had general, one (20) lung-, two (15 and 16) liver-, two (7 and 27) mediastinal, two others (8 and 18) retroperitoneal and six (4, 8, 15, 21, 27 and 28) peritoneal metastases. Two cases (7 and 17) have had large epigastric tumours.

Another clinical feature which may be of diagnostic value is the presence of so high amounts of gonadotropic hormones in the urine, as to even give a positive Ascheim-Zondek test. However, in most cases no hormones could be found (R. MEYER, KLEIN, FRANKL, FAUVET, FÖDERL and others), and quantitative assay has seldom been reported. When the value has been given, it has been under 200 M.U. prolan A per liter urine. (WALLIS, 150—200 units, HOHAGE 110 units.) On the other hand, FAUVET found in one case large amounts of prolan A before, and of prolan A and B after the operation, and in some cases in the literature the Ascheim-Zondek test has been positive (CHRISTIDI and FAGARASANU, STOIA, STANCIULESCU and CIOC, BARZILAI). SPIELMAN and MORTON, have in one case studied the hormal content of the tumour and found 60 R.U. of prolan A therein, whereas ZONDEK, 1937, was unable to find any gonadotropic substances in assays on tumour tissue.

Hormonal assays have only been performed in one case in this material, case nr 35. This case, however, is in this respect of special interest, as, on behalf of repeatedly positive Ascheim-Zondek tests together with amenorrhea and enlarging pelvic resistance the patient was considered pregnant for five months. During this time these tests were positive four times (the last seven days before operation), and negative only once. An assay on urine taken 11 days before operation (when the tumour was of the size of more than a mans's head), showed < 110 M.U. folliculin and $> 1{,}000$ M.U. prolan A and B of chorion type per liter urine. Three weeks after the operation the Ascheim-Zondek test was negative and a urinal assay showed 500 M.U. prolan A per liter.

This rather unique case has been thoroughly histologically investigated in order to exclude the possibility that the tumour could contain also choriomatous parts. Only typical and pure dysgerminomatous structures were found in all parts. Together with the cases in the literature which have shown high amounts of prolan A (or positive Ascheim-Zondek tests), this case gives support to the earlier mentioned assumption made by TEILUM regarding the close histogenetic relations between the dysgerminomas and the ovarian choriomas.

Pathology

The dysgerminoma is sometimes bilateral. Otherwise it seems to show a predilection for arising in the right ovary (SEEGAR and others). Four of the 37 cases in this material had bilateral growths (4, 15, 16 and 34) and 25 had a right-sided tumour. If these cases are counted together with the cases in the literature, where the location is mentioned, the tumours were in 51 % located in the right ovary, in 32 % in the left and in 17 % bilateral. (See Table IV.)

Table IV.

Location of tumour.

	Location		
	Right ovary	Left ovary	Bilateral
Cases (Radiumhemmet)	25	8	4
Cases (Literature)	79	58	32
	104 (51 %)	**66** (32 %)	**36** (17 %)

This predilection for the right ovary has probably some bearing on the histogenesis of these tumours. It is known from both embryological

and comparative anatomical observations that the differentiation of the ovarian tissue on the right side proceeds more slowly and to a less degree than it does on the left side (cf. POPOFF and others). Thus, if undifferentiated, totipotent embryonic tissue remains behind, the probability of its occurrence in the right ovary ought to be greater than in the left. The predilection of dysgerminomas for the right ovary is, therefore, in accordance with the histogenetic theories of teratoid origin for these tumours.

Macroscopically the tumour, if of larger size, is in general rounded with smooth or coarsely lobulated surface and is enclosed in a fibrous capsule that remains intact in the early stages but sometimes ruptures in the advanced stages (see above). The consistency varies from hard, rubbery in smaller tumours to spongy and friable in larger ones on account of extensive secondary changes with often large necroses. On cut surface, the tumour appears of a greyish-pink colour, often with areas of a distinctly yellowish hue. The tumourmass is, as a whole, rather homogeneous. Strands of fibrous tissue may, however, divide it into lobules.

Microscopically there are few tumours of the ovary which present such distinctive characteristics as does dysgerminoma. This applies to both the cell type and the general architecture. For this reason, the microscopic recognition is usually easy and the differential diagnosis can mostly be made without difficulties, an advantage enjoyed by few ovarian tumours.

The dysgerminoma cells are markedly uniform, rather large, round or polyhedral and have a moderate amount of granular or clear, often translucent cytoplasm, containing relatively large amounts of glycogen. The nuclei are large, vesicular with thick nuclear membranes. (See Fig. 6.) They are rich in chromatin and have usually more than one well developed highly basophilic nucleolus. The cells obviously have a high content of fluid. Mitotic figures are present in varying, often large numbers.

The structure of the cells is suggestive of cells in rapid proliferation, in good conformity with the earlier mentioned clinical features which strongly suggest a very rapid tumour growth. Also studies of the protein metabolism and the closely associated nucleic-acid metabolism in the cells with the use of special methods (performed in case nr 28) demonstrate that the cells are characterized by an intensely active functioning system of protein formation, inasmuch as they possess a high content of nucleotides in the nucleus, especially assembled in the large, well developed nucleoli and along the thick nuclear membranes. (See Fig. 6.) (For details regarding these special methods and the significance of the findings obtained with them, see CASPERSSON and SANTESSON, 1942.)

The arrangement of the tumour cells is rather characteristic, although it varies even in different parts of the same tumour. The cells are arranged either in single-layered columns or in strands (see fig. 3), in small acini-like groups or larger irregular nests of cells, separated by a more or less abundant and usually delicate network of connective tissue stroma (see figs. 1, 2, 5, 7). Sometimes, especially in central portions of larger tumours, the cells assume a medullary pattern with diffuse cell arrangement and only scanty supporting connective tissue stroma. A most prominent feature is that the stroma is mostly abundantly infiltrated with lymphocytes (see figs. 1, 2, 4, 5, 7), which sometimes even form actual lymph follicles with a distinct germinal center.

The dysgerminoma cells, on account of their high content of fluid, do, however, very easily undergo marked shrinkage. For this reason, the cells in material treated in the usual manner, *i. e.* fixed in formalin and embedded in paraffin, appear shrunken with indistinct cell borders and only a thin halo of crumpled cytoplasm and are usually completely

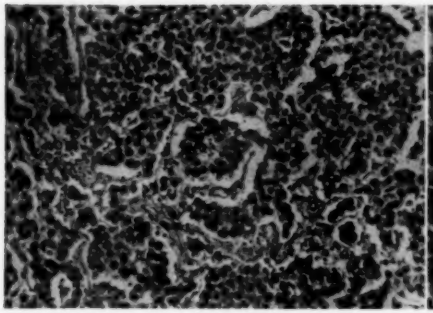

Fig. 1.

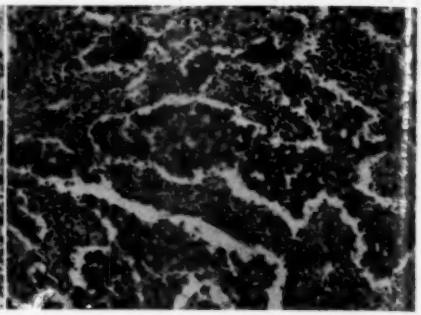

Fig. 2.

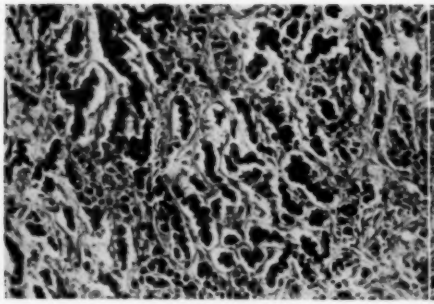

Fig. 3.

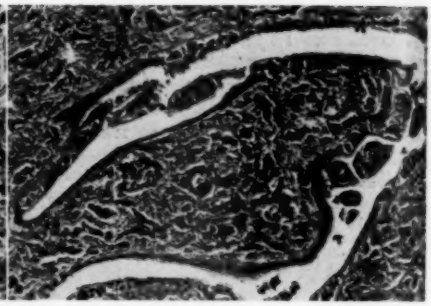

Fig. 4.

Fig. 1. Case 2. Tumour tissue divided into nests or islands of cells by strands of connective tissue, rather markedly infiltrated with lymphocytes. Magn. 165.

Fig. 2. Case 17. Tumour tissue divided in larger acini-like groups of cells by delicate network of connective tissue with some lymphocytic infiltration. Magn. 165.

Fig. 3. Case 26. Tumour cells arranged in single-layered columns or strands. Scanty lymphocytic infiltration in the stroma. Note shrinkage of cells and columns. Magn. 165.

Fig. 4. Case 26. Tumour tissue infiltrating in the folds of the tubal mucosa. Magn. 97.

detached from the stroma as well as separated from one another, appearing as isolated cellular elements (see figs. 1, 2, 3 and 7). This detachment and isolation of the cells constitutes another characteristic feature, which even has been considered of diagnostic significance. The true aspect of the cells and of their relation to the stroma is seen only in frozen sections or in material immediately fixed after removal in special fixative.

Regressive changes are so frequent and often so extensive as to constitute another specific feature of the tumour. They consist in a progressive acidophilic necrobiosis with fatty degeneration or intracellular calcification and finally necrosis. Marked such changes are found in the two cases in this material that have obtained preoperative roentgen treatment (7 and 35) and which during and following these treatments markedly dimin-

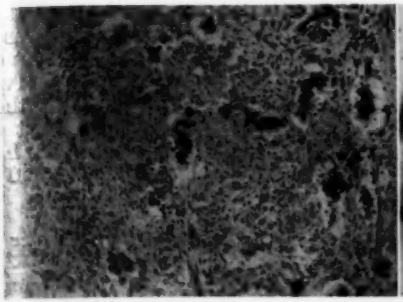

Fig. 5.

Fig. 6.

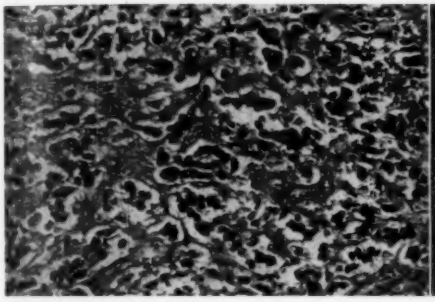

Fig. 7.

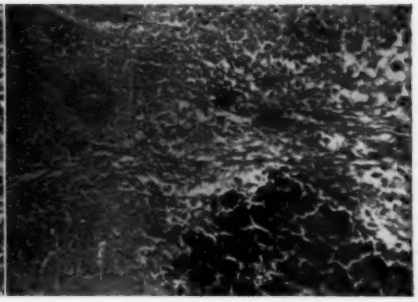

Fig. 8.

Fig. 5. Case 13. Tumour tissue divided in small nests of cells by abundant, rather firm connective tissue with some lymphocytic infiltration. Magn. 165.

Fig. 6. Case 28. Tumour cells inside bloodvessel. Photography of unstained slide in *ultraviolet light* at the wave length 2,570 Å. Magn. 2,400×. Objective aperture 0.85. Condenser aperture 0.6. (See text.)

Fig. 7. Case 7. Tumour preoperatively radiated. Rest of tumour tissue growing in small strands divided by rather firm connective tissue with some lymphocytes. Note shrinkage of cells and strands. Magn. 165×.

Fig. 8. Case 7. Tumour preoperatively radiated. Necrotic, in lower right corner calcified area. To the right collections of lipoidophages. Magn. 165×.

ished. The tumour in the first case contains numerous, partly large, necrotic, here and there calcified areas (see fig. 8). Particularly around these areas are found collections of lipoidophages. The bulk of the tumour is composed of partly loose and oedematous, partly firm more or less hyalinized connective tissue. This fibrotic tissue is obviously the end result of the marked regressive, necrobiotic changes caused by the roentgen treatment. Only in some small parts there are a few remaining strands of cells with an arrangement and structure typical of dysgerminoma cells (see fig. 7). (The tumour in the other case shows similar but less pronounced changes.)

Another feature peculiar to this tumour is the occurrence, usually in areas showing regressive changes, of nests of tubercle-like granulation tissue sometimes containing giant

cells resembling the Langhans cells of tuberculosis. Also in some of the tumours in this material such nests are to be found. Their occurrence was in earlier times considered as a sign of coexistence of tumour and tbc (KERMAUNER and others), and, in reality, cases of dysgerminoma together with tbc have been described (V. SZATHMARY, HANSEN). (Two such cases, nr 5 and 9, are, furthermore, to be found in this material.) Later, on the other hand, SCHILLER has advanced the view that the epithelioid and giant cells are not of tuberculous origin but are reactive to degenerative changes in the tumour. This view has been generally adopted (FÖDERL, NOVAK and GRAY, HANSEN, HELLER and others) and is in accordance with the findings in this material.

The histological structure of dysgerminoma is undoubtedly that of a malignant tumour. The degree of malignancy has, however, been considered variable by many authors and some have attempted to draw conclusions as to this degree from the microscopic pattern of the tumour. Thus, FAUVET has suggested that tumours showing predominance of dysgerminoma cells and paucity of connective tissue are more malignant than those with bulky stroma and few tumour cells. SEEGAR, on the other hand, in 14 cases of his material, tried, but with negative result, to find a correlation between the degree of malignancy and the amount of mitotic figures in the tumours and FÖDERL believed that the prognosis could be estimated on the degree of infiltration in the adnexal tissue and of necrobiotic changes observed in the tumour cells which had broken into lymph- and blood-vessels. Other authors have, however, not been able to find any of these criteria to be of definite value. The same has been the result of attempts to apply these or other histologic criteria on the tumours in this material.

Prognosis and Treatment

The prognosis in cases of dysgerminoma has been much disputed and in earlier years very different opinions in this respect have been presented on account of the small series of cases reported and adequately followed. In later years there seems to be general agreement that the prognosis must be considered as serious, although not as bad as in cases of histologically clearly malignant ovarian carcinomas (FÖDERL, NOVAK and GRAY, RUSSEL, SJÖVALL, BARZILAI and others). The number of cases in the literature followed over 5 years is, however, still rather small. Thus, of the 98 cases studies by SEEGAR in 1938 (79 collected from the literature, together with 19 cases of his own), there are only 40 cases in which the five-year results can be studied and among 192 cases assembled from the literature by the author, there are only 80 such cases.

It is to be noted that as regards this type of tumour the five-year results seem to be significant for judging the prognosis as in 38 cases (27 assembled from the literature and 11 of the authors) which have died apparently from the effects of the tumour and for which the time of

death (postoperative deaths not included) can be ascertained, all, except one case, have died less than five years after the operation, 24 of them even within one year.

As has already been pointed out, it has not been found possible to judge the prognosis from the histological structure of the tumour. It seems, on the other hand, that a rather reliable prognostic judgement can be based on the extension of the tumour process observed at operation. If the cases, as NOVAK and GRAY have suggested, are divided partly in those with tumours still confined to the ovary and with intact tumour capsule and partly in those with extension outside the ovary or with ruptured capsule, it is found that of 61 cases (39 from the literature and 22 from this material) belonging to the first type 49 are living over 5 years and the rest have died from the tumour, while of 28 cases (21 from the literature and 7 from this material) belonging to the second type 24 have died from the tumour and only 4 are living over 5 years.

Table V shows the mortality as judged from 192 cases assembled from the literature and from the 37 cases in this material.

Table V.

Mortality.

	Dead			Alive			
	Post-operative Deaths	Deaths from Tumour	Deaths from other Causes	Under five Years	5—10 Years	Over ten Years	Not traced
Cases (Radiumhemmet) 37	0	11	1[1]	8	9[2]	9	—
Cases (Literature) 192	12	31	2	62	25	12	48

As can be seen in the Table there are among the 192 cases assembled from the literature only 80 for which five-years follow-up data are given. Of these 80 cases 43 have died (12 directly in connection with the operation and 31 apparently from the effects of the tumour). Of the 27 cases treated at Radiumhemmet more than five years ago 9 have died from the tumour. The survival rate in all these cases is, thus, 55 cases of 107, *i. e.* 51.4 %. (For the cases of Radiumhemmet treated more than five years ago this rate is 18 cases of 27, *i. e.* 66.7 %, and the three-year survival rate is 20 cases of 31, *i. e.* 64.5 %.)

In later years there seems to be general agreement that radical surgical removal of the tumour, followed by radiotherapy is the treatment of choice for dysgerminomas. There are, however, different opinions as regards the necessary extensiveness both of the operation as well as of the

[1] Through traffic accident. Symptomfree 8 years (14).

[2] Two cases lost track of after 7 years (1, 11.) Included among the cases alive 5—10 years.

radiological treatment. Most authors consider that if the tumour at operation is found to be confined to the ovary, conservative surgical procedure with only radical excision of the tumour is justified. Such a conservative procedure is obviously desirable in these mostly young patients in order to preserve the functions of the other ovary and, thus, also the possibilities for future pregnancies. (FÖDERL, SEEGAR, NOVAK and GRAY, HÜCKEL, SAILER, NORDMEYER, DUPONT, POTTER and others.) On the other hand, some authors have also in such as yet simple cases considered a radical procedure with bilateral oophorectomy and hysterectomy advisable on account of the great risk of recurrence especially in the other ovary if a conservative procedure is used. (KIRSCHBAUM and NEWMAN, SJÖVALL, BARZILAI, SELBYE and others.)

Already in 1921 BECLÈRE reported a case of dysgerminoma which showed a high roentgen sensitivity and in the following years further such cases were described, especially by French authors (PROUST, DELBET, HOCHE, HAJEK, DOUBRÈRE, GILLIARD, KLEINE and others). It has, however, only in later years been generally recognised that these tumours show similar great roentgen sensitivity as the corresponding testicular seminomas and that postoperative radiological treatment not only can cure those cases in which radical operation cannot be accomplished but also ought to be used as a prophylactic measure against recurrences following radical surgical removal of the tumour. Yet, there seems not to have been made any definite effort on the part of gynecologists to treat these cases adequately with radiation, although there are many reports of rapid regression of recurrent conditions under radiation.

As regards the necessary extensiveness of the prophylactic radiological treatment in radically but conservatively operated cases, there are also different opinions according to the views of the respective author concerning the risk entailed in sparing the unaffected ovary as compared with the desirability of preserving its function. Some of the authors which advocate a conservative surgical procedure (see above) also find it advisable to take the risk not to give roentgen on the unaffected side, while others consider the risk of recurrences too great and for this reason find it justifiable to use a radical radiological procedure.

It would, thus, be of great interest to find out the risks in comparison with the gains entailed in the conservative mode of surgical and radiological treatment. The number of cases in the literature treated in this manner and with adequate clinical histories as well as follow-up data over five years is, however, as yet so small that any definite judgement of these questions cannot be obtained. On account of the obvious importance of these questions, the author has, still, found it warranted to review here the results obtained in the conservatively treated cases, in the hope that this review might be of value.

In the cases assembled from the literature, there are 39 conservatively operated and not radiologically treated cases with adequate histories and follow-up data for more than 2 years. Of these 34 have lived (18 more than five years and 16 from 2—5 years) without any recurrences, while 5 have got recurrence in the other ovary. (Two of these cases have lived more than five years and three have died from the tumour.) On the other hand, there are 8 conservatively operated cases which have obtained postoperative roentgen treatment also on the unaffected side. Of these 6 have lived over five years, one two years and one has died from recurrences, although not in the other ovary.

Among the five-year cases in the material of Radiumhemmet, there are 16 conservatively operated cases (of which 14 are living) and 6 (2, 6, 17, 20, 22 and 23) of these have not obtained radiological treatment directly after the operation on the unaffected side. Two of these cases (17 and 22) got recurrence in this side and three (2, 6 and 20) as well as two other cases (10 and 18) got recurrences elsewhere than in the other ovary. (The cases 18 and 20 have died from the tumour.)

There is, thus, only 24 (18 from the literature and 6 from this material) conservatively treated five-year cases and of these 7 have later got recurrence in the untreated ovary. Three of these 7 cases have died from the tumour. 18 cases (8 from the literature and 10 from this material), which were conservatively operated, have obtained radiological treatment directly after the operation also on the unaffected side. None of them has got recurrence in this ovary. Two of these cases have died from the tumour, one is living three years and the rest over five years after the operation, although two have got recurrences elsewhere than in the ovary unaffected at the operation.

Of the above mentioned 39 conservatively treated cases from the literature 9 cases and among the 6 cases of Radiumhemmet two (6 and 23) have been pregnant with deliveries of normal children after the operation. Of the 18 conservatively operated but radically irradiated cases there are three (two of them, 3 and 25, from this material) which have been pregnant despite the radiological treatment on the ovary left at the operation. (Case 3 got abortion 13 years and case 25 delivered a normal child $2^1/_2$ years after the operation.) As regards the function of the ovary which was left at the operation, it is of special interest to note that of 15 cases in the material of Radiumhemmet in all except two (12 and 27) the menstruation have returned after the operation, although 11 of them (3, 9, 10, 11, 12, 14, 19, 25, 27, 30 and 32) were irradiated also on this ovary directly after the operation and three others (2, 6 and 17) later, when clinical recurrences were noticed at control examination.

Although, as is already pointed out, the number of cases is still too small to allow any definite judgement of the risks as compared with the gains entailed in the conservative mode of surgical and radiological treatment, the findings of the review given above seem the author to point in the direction that a conservative surgical procedure is warranted only if it is followed by radical radiological treatment, *i. e.* prophylactic radiation also against the ovary unaffected at the operation. The percentage of 7 cases with recurrence in this ovary among 24 in both respects conservatively treated cases seems to be rather high. The review shows, on the other hand, that radical prophylactic radiological treatment, given in the right manner, does not impair the functions of the unaffected ovary left at the operation. Thus, in such cases the menstruations mostly return and even pregnancies with the birth of normal children may occur.

In the following some points of interest especially in the material of Radiumhemmet will be discussed. It is to be noted that nearly all the cases in this material have been operated elsewhere and then referred to the Radiumhemmet for postoperative radiological treatment. It is, furthermore, of importance to mention that most of the cases from earlier years have at the time of treatment been wrongly diagnosed and treated as some type of ovarian carcinoma. Only in the cases from later years the tumours have from the beginning been diagnosed as dysgerminomas and in these cases a somewhat similar type of radiological treatment has been given.

Five fields of treatment have mostly been used, one abdominal field and one on the back against the pelvic region on each side and one central field against the upper part of the back up to the diaphragm. This last field is of special importance in the prophylactic roentgen treatment on account of the fact that these tumours at first mostly metastasize to the retroperitoneal lymph nodes along the big abdominal vessels (see page 655). The doses have mostly varied from 400 to 600 r units given in separate treatments of from 100 to 300 r units with 0.5 mm. Cu as filter. On the field over the upper part of the back the doses have been somewhat smaller.

The importance of a radical extirpation of the tumour at the operation is clearly shown by the results in this material. In 11 cases (4, 7, 8, 15, 16, 21, 24, 27, 28, 29 and 30) radical extirpation could not be accomplished. 9 of these cases have died from the tumour and only two (27 and 29) are living, case 27 $5^1/_2$ and case 29 $3^3/_4$ years after the operation. The serious consequences of a rupture of the tumour before the operation have already been pointed out (see page 655). The prognosis in cases with bilateral tumours is very serious. Of the four such cases in this material (4, 15, 16 and 34) the first three have died. (Radical extirpation was not possible in any of these cases.) The last case (34), where the operation was considered radical is newly operated (living symptomfree only 10 months). In 14 of the 32 cases in the literature with bilateral tumours a follow-up more than three years is given. 9 of these 14 cases have died and 5 are living, one three years, another four and the others more than five years after the operation.

Radical extirpation of the tumour was possible in 26 cases in this material. 8 of these cases (2, 5, 6, 10, 17, 18, 20 and 22) have sooner or later got clinical recurrences. Two of them (18 and 20) have died from the tumour. The remaining 6 cases have been cured by the radiological treatment and are living symptomfree from $7^1/_2$ (case 22) to 24 years (case 2) after the operation. The time for the appearance of the clinical recurrences has in these 8 cases varied from two months to $2^1/_2$ years. (In case 17 this time was $2^1/_2$ years, in the other cases one year or less.) In cases 17 and 20 new recurrences appeared after a symptomfree period of $3^1/_2$ years and 9 months respectively. In the 11 incompletely operated cases, on the other

had (see above), the time for the appearance of the clinical recurrences was from one month to four years. (In cases 24, 8, 28, 15, 21 and 30 this time was from one month to nine months, in cases 7 and 27 three years and in cases 4 and 16 four years.) It seems safe to assume that in the last mentioned four cases (4, 7, 16 and 27) the radiological treatment has given the patients a symptomfree life-time of three and four years respectively. (Case 27 is still living and symptomfree $5^1/_2$ years after the operation and one year since the appearance of the last recurrences. Case 29, furthermore, had recurrences at the beginning of the postoperative roentgen and radium-treatment. These disappeared after the treatment and the patient is still living and symptomfree $3^3/_4$ years after the operation.)

Thus, the radiological treatment has obviously cured 6 radically operated cases from their later appearing clinical recurrences and lengthened the life-time of four incompletely operated cases from three to four years. It has possibly also cured one of these last cases as well as one other incompletely operated case. It seems, furthermore, probable that the radiological treatment also has hindered recurrences to appear in at least a few of the 11 cases (1, 3, 9, 11, 12, 13, 14, 19, 23, 25 and 26) which have been symptomfree more than five years since the operation.

It may finally be of interest to make a comparison of the results in the cases assembled from the literature which were only operated and not radiologically treated with the results in those cases which also have obtained radiological treatment. The number of reported cases, treated in these different ways is, however, still so small that any definite judgement cannot be obtained from a comparison of this type.

As already has been mentioned (see page 661), the survival rate in all the cases (from the literature and in this material) with five-year follow-up data is 55 cases of 107, *i. e.* 51.4 %. (In the cases of Radiumhemmet this rate is 18 cases of 27, *i. e.* 66.7 % and the three-year survival rate is 20 cases of 31, *i. e.* 64.5 %.) Among the cases assembled from the literature there are only 21 operated and radiologically treated cases for which five-year results are given. 12 of these have lived over five years, *i. e.* a survival rate of 57.1 %. If these cases are counted together with the cases in this material, the survival rate is 30 cases of 48, *i. e.* 62.5 %. There are, on the other hand, 48 cases in the literature with five-year follow-up data which cases according to the given clinical histories have only been operated and not radiologically treated. Of these 48 cases 20 have lived over five years, *i. e.* a survival rate of 41.7 %. Although these figures concern only a small number of cases, they obviously indicate how important the radiological treatment is in order to obtain the best results in cases with dysgerminomas.

Main Results

This paper gives the first part of a clinical and pathological survey of about 700 cases of ovarian tumours treated at Radiumhemmet until and including 1940. In this first part the data on 26 cases of dysgerminoma, occurring among these cases of ovarian tumours, together with the data on 11 cases treated in later years, are surveyed. Furthermore, the data on 192 cases assembled from the literature are reviewed. Only those cases are included which in all respects and exclusively show histological structures typical for this rather rare type of ovarian tumour. The incidence of pure dysgerminomas in the whole material of ovarian tumours at Radiumhemmet is 3.7 %. For 27 of the 37 cases of dysgerminoma at the Radiumhemmet five-year results are available.

The clinical features are described and the histogenetic questions discussed. The dysgerminoma predominantly occurs in young persons. In the whole material of 229 cases the age incidence is 81 % under thirty and 44 % under twenty years of age. The location, mentioned in 196 cases, was in 51 % in the right ovary and in 17 % bilateral. In the material of Radiumhemmet nothing new has come forth as regards the macro- and microscopical characteristics of these tumours. The author has not been able to find any histologic criteria of value in order to judge the degree of malignancy and to estimate the prognosis. It seems, on the other hand, that a rather reliable prognostic judgement can be based on the extension of the tumour process observed at operation.

In the cases of Radiumhemmet especially the prognosis as well as the results of and other questions in connection with the radiological treatment are more thoroughly surveyed. In 107 cases (80 from the literature and 27 from this material) five-year follow-up data are available. The survival rate is 55 of these 107 cases, *i. e.* 51.4 %. This rate for the cases at Radiumhemmet is 18 cases of 27, *i. e.* 66.7 % and the three-year survival rate is 20 cases of 31, *i. e.* 64.5 %. The five-year results seem to be significant as regards this type of tumour. Radical surgical removal of the tumour followed by radiotherapy is the treatment of choice. Conservative operative procedure with removal only of the affected ovary followed by prophylactic radiological treatment against both pelvic regions and against a central field on the back up to the diaphragm seems to give the best results. The findings at a survey of the whole, still very small, available material indicate that if the ovary left at operation is not irradiated the risks of recurrence in this ovary are rather high. Such treatment, on the other hand, does not for the future markedly impair the functions of this ovary. It is of serious consequences if the tumour is not radically extirpated and if a rupture of the tumour has occurred before the operation.

The prognosis in cases with bilateral tumours is very serious. A comparison of the results in only operated cases with those in also irradiated cases, possibly on a very limited number of patients only, shows about 20 % better five-year survival rate for the radiologically treated cases.

SUMMARY

This paper gives the data on 37 cases of pure dysgerminomas radiologically treated at Radiumhemmet, Stockholm, for 27 of which five-year results are available. Furthermore, the data on 192 cases of dysgerminomas assembled from the literature are reviewed. The clinical features and the pathological characteristics of these cases are described. The prognosis and the results as well as questions in connection with the radiological treatment are more thoroughly dealt with.

ZUSAMMENFASSUNG

Diese Arbeit gibt eine Zusammenstellung der Befunde bei 37 Fällen von in Radiumhemmet, Stockholm, radiologisch behandelten reinen Dysgerminomen, darunter 27 Fälle mit fünfjährigen Ergebnissen. Ausserdem wird eine Übersicht über 192 aus dem Schrifttum zusammengestellte Dysgerminomfälle gegeben. Die klinischen und pathologischen Kennzeichen dieser Fälle werden beschrieben. Eingehender werden Prognose und Resultate sowie mit der radiologischen Therapie zusammenhängende Fragen besprochen.

RÉSUMÉ

Ce mémoire collationne les constatations faites dans 37 cas de dysgerminomes purs traités par les rayons au Radiumhemmet, Stockholm, chez 27 desquels on connaît le résultat au bout de cinq ans. En outre il apporte une revue de 192 cas de dysgerminomes de la littérature. Description des caractères cliniques et pathologiques de ces cas. Le pronostic et les résultats, ainsi que des questions touchant la radiothérapie, sont traités de façon plus approfondie.

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FROM THE GENERAL DEPARTMENT OF RADIUMHEMMET, STOCKHOLM
(CHIEF: PROFESSOR ELIS G. E. BERVEN)

MALIGNANT TUMOURS OF THE TESTIS. TREATMENT AT RADIUMHEMMET, STOCKHOLM[1]

by

Hugo Ahlbom

Testicular tumours differ in several respects from other human tumours. They have therefore, particularly in relation to their rarity, attracted the attention of chiefly pathologists, surgeons and radiotherapeutists to an unusual extent. It is very interesting and instructive to study the scientific history of these tumours, especially concerning pathogenetic theories and pathologic-anatomic classification. In this paper, however, it will not be possible to mention more than a few of the more important historic items.

During the later part of the 19th century, a period of rapid progress of tumour pathology, the mixed or teratoid tumours of the testicle formed a favoured subject for studies and theoretic discussions. This tumour group was often used as an argument for the support of various general tumour theories. RIBBERT and WILMS were the most important contributors to the literature on testis tumours during this period and their conception of this tumour group and its position in the system of tumour pathology is still in its main parts accepted by most authors in this field.

In the early years of this century CHEVASSU in France and, later, EWING in U. S. A. completed the modern doctrine of testis tumours, especially regarding pathogenesis, histologic classification and clinical characters. CHEVASSU gave a very good and comprehensive histologic and clinical description of the tumors in question. He also clearly defined the interesting and quantitatively most important subgroup and gave it the name of seminoma. He considered the origin of the testis tumours to be the cells of the specific sex epithelium. EWING's classification is still used by many authors, especially in U. S. A. Many pathologists and clinicians use a more or less modified EWING classification. EWING con-

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sidered all the testis tumours to be mixed tumours. In the case of, or instance, the seminoma the epithelial cells were supposed to have co n-pletely overgrown the other elements.

The numerous papers dealing with this subject during the last thi ty years have added to our knowledge mainly in two ways. Firstly the methods of treatment — surgical as well as radiological — have b en gradually improved and the late results correspondingly more sa is-factory, secondly the investigations about hormonal excretion in ca ses with testis tumours (ZONDEK since 1929, and others) have opened a new field of research. At least according to some authors (FERGUSON, BANG, HAMBURGER and NIELSEN and others) the last mentioned research work has already led to practical results, particularly as an aid in the evaluation of the prognosis and the therapeutic results.

Besides the above mentioned special features of the testis tumours (concerning pathology and endocrinology) the following *clinical* characters are of particular interest:

1. The average *age* of patients with testis tumours is unusually low. Most authors agree that practically all the patients belong to the age group 20—50 years. In many of the published series the patients with mixed tumours were on the average about 10 years younger than the seminoma patients. The Radiumhemmet series which includes 65 seminomas and 44 malignant mixed tumours and adenocarcinomas shows an average of 39 years for the patients belonging to the first subgroup as compared to $30^1/_2$ years for the second.

The youngest patient with a seminoma was 18 years old, the oldest 69. The corresponding age figures for the mixed tumour and adenocarcinoma subgroup were 5 and 52 years.

2. *Trauma* has by several authors been considered to have more importance as an etiologic or predisposing factor where testis tumours are concerned than in most other tumour groups. Usually 10—20 % of the patients are said to have a history of trauma. A few authors who have published rather small series of cases mention trauma as even considerably more frequent than in 20 %. The frequency of trauma in our material was 15 %. Trauma to the testes is not at all unusual and, being rather painful, it is not so easily forgotten by the patients, even if relatively slight. The frequency of trauma among testis tumour patients does not seem to be high enough to be anything but incidental.

3. *Retention* of the testicle is a definite, statistically proved predisposing factor. According to GREVILLIUS who made a survey of the contributions to this question in the literature, tumours occur 40 times more frequently in abnormally than in normally situated testicles. The av rage frequency of testicular retention in the published series of testis tu ours was by GREVILLIUS found to be 13 %. Exactly that frequency wa also

found in our material (in 16 cases out of 119). Both in GREVILLIUS' and our series the kryptorchismus was relatively more frequent in the seminoma subgroup than in the other.

4. *Gynecomastia* in general is a relatively rare condition. It is mostly seen during and soon after puberty and often as a one-sided hyperplasia. In the form of 'ductal fibroadenomatosis' it also occurs in men of relatively high age (50—80 years), sometimes bilaterally. In the last mentioned cases the condition must be considered as a precancerous one. Among male tumour patients gynecomastia is otherwise seen only in cases of testicle tumours and in cases of carcinoma of the prostate treated over a long time with female hormones.

The gynecomastia connected with tumours of the testis is of course due to a disturbance, caused directly or indirectly by the tumour, in the hormonal production. In our series gynecomastia was found, usually several months after the operation, in 6 cases out of 119. The possibility of a higher frequency must be considered, because it is doubtful if the patients were regularly examined with regard to the presence of gynecomastia, especially during the earlier years.

If gynecomastia were a direct consequence of production of prolan due to the presence of the tumour, or of metastases after surgical removal of the tumour, it would be a sign of unfavourable prognosis and it would be found particularly in cases with a high rate of hormonal excretion. In our series no definite correlation to the prolan content of the urine could be shown. Gynecomastia was found in one case of seminoma where the patient afterwards was alive and well for more than 16 years. In one case of adenocarcinomatous mixed tumour the patient is alive and well 8 years after the operation. Of the six patients with gynecomastia only one had a seminoma, the other five tumours being of the mixed type.

The general opinion in the literature is that gynecomastia occurs very rarely in patients with testis tumours and is found most often in the exceptional cases of tumours resembling chorionepithelioma. The conditon may often be overlooked if a special examination is not routinely made at every follow-up visit. The patients themselves may be unaware of it.

5. *The radiosensitivity* of the seminomas is considered to be high by all authors of recent papers. The other microscopical types of testis tumours, on the other hand, are usually said to be only slightly radiosensitive. Our own experience is that some tumours belonging to the mixed tumour and adenocarcinoma subgroup have a radiosensitivity which comes very near that of the seminoma. The majority, however, have a moderate sensitivity, definitely lower than that of the seminoma but sometimes high enough to make a successful radiotherapy possible.

6. As the last clinical point I should like to mention the rather characteristic regions in which *metastases* of malignant testis tumours occur, if the patient is not cured at an early stage. On admission there were palpable metastases in the upper para-aortic lymph nodes (the typical 'first station') in 41 of our 119 cases. In the left supraclavicular lymph nodes metastases were palpable in 8 cases out of 119. Metastases in lungs, pleura, mediastinal lymph nodes, skeletal system, etc., were found only in rare cases, on clinical examination.

Inguinal metastases, also, are rare, a fact which seems to be much better known everywhere now than it was 10—15 years ago, when patients could be seen who had received inguinal irradiation only, after orchiectomy.

Treatment

Among the numerous different methods of treatment described in the literature the following three main principles may be distinguished.

1. *Radical surgery*, including removal of the retroperitoneal lymph nodes. This difficult operation has been worked out by CHEVASSU and HINMAN and is in use at a few clinics (KELBY and STENSTRÖM, and others) probably only for the less radiosensitive tumour types. The radical operation is sometimes combined with postoperative roentgen treatment.

2. *Simple orchiectomy*, usually followed by roentgen irradiation. This method seems to be favoured by the majority of recent authors, especially regarding the seminomas.

3. *Primary irradiation*, either given routinely as a preoperative treatment followed later by orchiectomy (CHAMBERLAIN and JAMISON, and others), or, in the case of the radiosensitive tumours, without surgical intervention.

At Radiumhemmet the principle of orchiectomy followed by roentgen treatment of the upper para-aortic lymph nodes has always been applied.

The surgical removal of the primary tumour is an unusually simple procedure and it is usually possible to remove the tumour without cutting into tumour tissue. Furthermore, the orchiectomy has the advantage that material for microscopic diagnosis and classification is obtained. The operation, finally, makes it unnecessary to irradiate with large doses the sensitive tissues of the scrotum.

Metastases, in the form of a rounded, flat, often large resistance palpable in the upper part of the abdomen on the side of the primary tumour, were found in about 40 % of the operated cases when the patients came for postoperative roentgen treatment. The actual frequency undoubtedly was higher, as there must have been cases with only microscopic or small, still not palpable lymph node metastases. The most im-

portant problem for the radiologist therefore is to give a considerable total dose of roentgen rays to this lymph node region soon after the orchiectomy. Roentgen sickness often causes difficulties even if a moderate daily dose, such as 250 or 300 r is being used.

In about 45 % of the cases in our series roentgen was also given on the inguinal region and the iliac fossa on the tumour side. This was particularly done in cases of large, infiltrating primary tumours which were more often seen during the earlier years than later.

Several authors have suggested prophylactic roentgen treatment over wide areas of the body, for instance the inguinal region, abdomen, mediastinum and left supraclavicular region. We have always felt that such a 'subtotal' irradiation involves risks for the patient's general resistance, his blood etc. The published reports about cases treated with the mentioned technique have not shown particularly good results. According to a recently published investigation by MOSSBERG, there must be a certain risk of thrombocytopenia and haemorrhagic diathesis with treatment according to this method, at least when relatively large doses are given over the mediastinal nodes and the upper part of the abdomen. We feel that a relatively large dose concentrated on the para-aortic lymph nodes is the best method and our late results seem to support this opinion.

Usually one anterior and one posterior field have been used, the size of each field being 300—400 cm^2.

The tubes are run with about 180 kv and 6—20 ma. The focal distance in the earlier years was 30 or 40 cm, now usually 50—60 cm. The filters mostly used are Thoræus' tin filter or $^1/_2$ mm Cu and 1 mm Al.

Treatment has been given daily, alternating on the two or three fields. The usual daily dose has been 300 r (back-scatter included).

During the last ten years the total dose has amounted to about 2,400 r (8 × 300 r) on each field. Earlier as a rule a smaller total dose was given (1,200—2,000 r).

Patients with metastases in other regions, for instance in mediastinum or supraclavicular lymph nodes, have received an individualized local irradiation for these metastases, usually with roentgen, in a few cases even with teleradium.

Results

Only microscopically verified cases were included in our series of 119 testis tumours and in all but a few cases professor O. REUTERWALL, chief pathologist at Radiumhemmet, reexamined the slides and classified the tumours. The three first of his four subgroups are: *seminomas* (65 cases), *adenocarcinomas* (24 cases), and *malignant mixed tumours*

(20 cases). The fourth subgroup consists of 10 cases of malignant tumour with rather varying histologic structure: There were found some sarcoma-like tumours and a few tumours with very low differentiation that could not be included in any of the other three subgroups. The average age of the patients in this last mentioned subgroup was relatively high. The tumours were clinically very malignant and the results of treatment rather poor.

The histologically different subgroups of adenocarcinomas and mixed tumours showed no significant differences concerning clinical characters, radiosensitivity and therapeutic results and I have therefore in the following tables brought them together.

Table 1.

	Number of cases	Alive and well more than five years
Seminomas	65	42 (about 65 %)
Adenocarcinomas and mal. mixed tumours	44	15 (about 35 %)
Sarcomatous and undifferentiated tumours	10	2
Total	**119**	**59** (about 50 %)

All tumours of the testis treated 1922—1941 incl.

Table 2.

	Number of cases	Alive and well more than five years
Seminomas	65	42 (about 65 %)
Other tumours	54	17 (about 30 %)

Comparison between the seminomas and the other tumours treated 1922—1941 incl.

Table 3.

	Number of cases	Alive and well more than five years
A. *No metastases on admission* (60 %) («prophylactic» roentgen treatment after orchiectomy).		
Seminomas	42	35 (about 80 %)
Other tumours	29	17
B. *Metastases on admission* (40 %).		
Seminomas	23	7
Other tumours	25	0

Comparison between the results in cases with and without metastases at the beginning of the roentgen treatment.

In the papers dealing with treatment of testis tumours it is not usual to find such accounts of the results that the 5 year figures can be determined. Moreover, as pointed out recently by SCHEETZ and LEDDY, there are many authors who have published their results in such a way that it is difficult or impossible to find out the relative proportion of seminomas and mixed tumours in the series, or the frequency of cases with metastases at the beginning of radiological treatment. Sometimes such a small number of cases is reported that the result figures have little value from a statistical point of view.

As far as I have been able to find the results of the Mayo Clinic are the best hitherto published. In 1938 LEDDY and DESJARDINS reported the following results after 5 years:

1. After simple orchiectomy: 40 %,
2. After orchiectomy followed by roentgen treatment: 53 %,
3. After roentgen treatment only: 14 %.

They calculated the cure-figures to be, for cases without metastases, 60 %, with metastases 32 %. The total number of cases in their series was 314. Histologic examination was made in 242 cases, showing seminoma in 76.

In 1939 the material of the Mayo Clinic was reviewed by CABOT and BERKSON. The best results were found in cases treated with orchiectomy and postoperative roentgen: In 45 cases of seminoma the result after five years was 71 % and in 29 cases of teratoma the corresponding figure was 29 %. An interesting statement was that 6 out of 12 patients with »massive metastases» of seminoma lived for five years after irradiation, and that 2 patients out of 13 with such metastases of teratoma also survived 5 years or more.

The results of other clinics have been considerably less favourable. Sometimes, for instance in the case of Memorial Hospital, New York City, the reason for the lower cure-rate was the unusually high frequency of advanced cases with metastases. (DEAN and others.) DEAN found metastases on admission in 72 % whereas our material at Radiumhemmet showed palpable metastases in only 40 %.

Considering the fact that the radical operation is not, of course, performed in cases with generalized metastases, which type of case is included in the radiotherapeutic reports, the result figures for this operation are remarkably low. HINMAN, who seems to be the only one who has published a somewhat larger series of radically operated cases, found a 5-year figure of only 21 % (in 80 cases).

It is interesting to note that we have had the same experience concerning the possibilities of a good and lasting result even in cases with massive metastases of seminoma, as have CABOT and BERKSON. Massive metastases of mixed tumours, however, which in two cases were treated

by the mentioned authors with a good effect, lasting at least five years, rarely disappeared completely after irradiation in our cases, and freedom from signs of tumour never lasted for as long a period as five years.

As seen from table 3 there were seven patients with metastases of seminoma alive and well after more than five years. These seven cases were rather advanced at the beginning of the roentgen treatment. Five of the patients had large abdominal metastases and have been well for 16 years (1 patient), 11 years (2 patients), 6 years (2 patients), respectively. One patient is well 13 years after roentgen treatment. He was subjected to laparotomy for an abdominal tumour before admission to Radiumhemmet. At the operation tumour masses were found growing extensively along the mesenterium and biopsy showed metastasis of seminoma. Finally one patient is alive and well 7 years after treatment for abdominal metastases and a large mass in the left supraclavicular region.

Apart from these remarkable results in advanced cases of seminoma, the palliative results obtained with roentgen treatment in all types of tumours of the testis demonstrate the value of radiotherapy in this tumour group. Many of our patients have had severe pain, etc. from abdominal or other metastases and been relieved for periods of usually 6—12 months from their subjective symptoms.

The prophylactically treated patients (without palpable metastases) have developed abdominal lymph node metastases in the subsequent course only in 9 cases (2 seminomas, 7 other tumours). The majority of the cases with a fatal course showed metastases in lungs, mediastinum, and the supraclavicular lymph nodes, but visceral and skeletal metastases also occurred. Inguinal metastases were subsequently observed only in two cases.

Conclusions regarding the treatment: 1. Orchiectomy followed by roentgen treatment to the lymph nodes is the most effective method when seminoma is concerned. Our experience shows that the same method should be preferred even in the treatment of mixed tumours and adenocarcinomas.

2. The good results of the Mayo Clinic (CABOT and BERKSON) were obtained by treatment according to the above mentioned principle but with postoperative roentgen treatment of a much wider area than in our cases. The fact that our results are well comparable with those of CABOT and BERKSON seems to indicate that a routine irradiation of mediastinum and the left supraclavicular region is not necessary. It is probably more important to give a rather large total dose to the para-aortic lymph nodes.

3. Inguinal metastases occurred subsequently in two of our prophylactically treated cases. Even if that is a very low frequency it is of

interest that none of these patients had received prophylactic treatment in the inguinal region. It is probably of value to extend the postoperative radiation even to the inguinal region on the tumours side, particularly if the primary tumour was large and infiltrating and the patient does not suffer too much from roentgen sickness.

4. In advanced cases of testis tumours with metastases it is usually possible to obtain a good palliative effect with irradiation. Especially in the seminoma subgroup it is even possible to obtain a lasting freedom from evidence of tumour in such cases.

Prolan excretion and prognosis.

FERGUSON, in his well known paper of 1934, reported very high values of prolan excretion with the urine from 37 patients with tumours of the testicle. For instance, in 15 cases of embryonal adenocarcinoma with lymphoid stroma, he found from 2,000 to 10,000 m. u. prolan A. He was convinced of the great value of prolan tests for the evaluation of the prognosis. During the following years several authors published their experiences but with very little conformity. A. BÉCLÈRE, GIBERT and HINGLAIS (1935) as well as (the same year) BANG, HAMBURGER and NIELSEN were convinced of the clinical value of prolan tests but had not so often seen cases with increased values as FERGUSON, nor so highly increased values.

NASH and LEDDY (1943) did not see much practical value in determination of the hormonal excretion in their cases. LOWRY, BEARD, HEWIT and BARNER (1946) went a step further and declared that their prolan tests had given no information of value.

Our experience has been about the same as that of the last mentioned authors. For about 10 years we sent samples of urine to different Swedish laboratories from our patients with tumours of the testicle. Prolan A and B tests were made once, twice or several times in altogether 59 of the 119 cases. In 44 of these the tests gave no information of value, in 9 cases only there was a slightly increased excretion found in patients who later died from metastases. The tests seemed to give information on the wrong side, finally, in 6 cases, as the patients remained free from metastases several years in spite of slightly increased hormone values during the first year after irradiation.

As high values as 400—500 m. u. were reported only in two cases, and no higher occurred. Usually the increased values were found to be about 80 m. u.

Blood sedimentation test and prognosis.

If the prolan tests, for reasons hitherto unknown, have proved a great disappointment to us, the technically much simpler sedimentation

test (carried out according to WESTERGREN's method) has instead been of definite value. The patients with testis tumours are relatively young and — disregarding the tumour — usually healthy men. They therefore as a rule show a normal sedimentation test when the primary tumour is removed and no metastases are present. We have found that it is a fairly reliable sign of good prognosis if the tests, which should be carried out at every follow-up examination, remain within normal limits during 2—3 years after the orchiectomy.

If there appears a tendency towards gradually higher values, this is usually a foreboding that pains or other symtoms of metastases can be expected. In such cases we reduce the intervals between the follow-up visits in order to be able to give treatment at as early a stage as possible.

Of 30 patients which remained well after orchiectomy and irradiation only 7 showed an increased sedimentation rate. The other 23 patients had normal values. Of the 7 patients three had a possible 'other' explanation of their increased sedimentation values (chronic bronchitis in one case, arthritis in one and gastric carcinoma in one).

In cases with metastases the sedimentation values as a rule exceeded 25—30 mm in one hour and there was a clear correlation between the general and local status of the patient on one side, and the sedimentation values on the other side: These values decreased during and after a successful palliative roentgen treatment, etc.

SUMMARY

From 1922 to 1941 incl. 119 patients with malignant tumours of the testis were treated. The results after five years for the whole series was about 50 %, in cases without metastases about 70 %. The result after five years was about 65 % for the seminomas (65 cases) and about 35 % for the adenocarcinomas and mal. mixed tumours (44 cases). The seminomas without metastases showed a five year cure rate of about 80 %. Orchiectomy and postoperative roentgen treatment, chiefly on the para-aortic lymph nodes, is considered the best method. Practically no information regarding the prognosis was obtained from prolan tests made in 59 cases. Blood sedimentation tests seem to be of particular prognostic value in this tumour group.

ZUSAMMENFASSUNG

Von 1922 bis 1941 einschl. wurden 119 Kranke mit malignen Testistumoren behandelt. Die Ergebnisse nach fünf Jahren waren für die gesamte Serie etwa 50 %, für Fälle ohne Metastasen etwa 70 %. Das Ergebnis nach fünf Jahren war für die Seminome (65 Fälle) etwa 65 %, für die Adenokarzinome und malignen Mischgeschwülste (44 Fälle) etwa 35 %. Die Seminome ohne Metastasen gaben fünfjährige Heilung in etwa 80 %. Orchidektomie und postoperative Röntgenbehandlung, besonders der paraaortischen Lymphdrüsen, dürfte die beste Methode sein. Durch Prolanprobe an 59 Fällen wurden praktisch keine Auskünfte über die Prognose erhalten. Die Blutsenkungsreaktion scheint bei dieser Gruppe von Tumoren von besonders grossem prognostischem Wert zu sein

RÉSUMÉ

De 1922 à 1941 inclusivement on a traité 119 malades atteints de tumeurs malignes du testicule. Les résultats favorables après cinq ans ascendent à 50 % pour toute la série, et à environ 70 % pour les cas sans métastases. Ils sont, après le même laps de temps, d'environ 65 % pour les séminomes (65 cas), et d'à peu près 35 % pour les adénocarcinomes et les tumeurs mixtes malignes (44 cas). Les séminomes sans métastases ont donné un pourcentage de guérison après cinq ans de 80 % approximativement. L'ablation du testicule suivie de radiothérapie post-opératoire, principalement au niveau des ganglions lymphatiques para-aortiques, est considérée comme la méthode la meilleure. Pratiquement on n'a pas obtenu de données utilisables pour le pronostic de la recherche du prolan, faite dans 59 cas. La mesure de la vitesse de sédimentation semble avoir une valeur pronostique particulière dans ce groupe de tumeurs.

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THE PROPHYLAXIS OF RECURRENT CARCINOMA OF THE VULVA[1]

by

Percy Malpas

The general principles by which an early cancer of the vulva should be treated are now well established, in the main as the result of the pioneer work of BASSET (1), TAUSSIG (8), STOECKEL (7), BLAIR BELL and DATNOW (3), BERVEN of Radiumhemmet (2), to name some of the outstanding contributors to our knowledge. There is a general agreement that in operable cases the primary lesion should be treated by a vulvectomy, perhaps preceded by an initial radiation, and that the lymphatic glands and lymphatic drainage areas should be dealt with either by a bilateral block dissection or by adequate irradiation followed in some cases by a gland dissection.

On a priori grounds the results obtained by so treating operable lesions should be excellent. For the most part these growths occur in older women in whom the momentum of spread of cancer is slower than in the young; there is no question of conserving any tissue or organ necessary to life; treatment can be as radical as desired and the patient's condition permits. Yet despite these considerations even the best published series of end-results show a high proportion of failures. BERVEN in his paper published in 1941, »177 Fälle mit Primarem Vulvakarzinom» (2), one of the most authoritative papers on the subject, states that according to comprehensive collective statistics the percentages of five year cures range from 4—10 %, though some hospitals report 5-year cures in 17—35 %. TAUSSIG (8) gives a 5-year cure rate of 58.5 % in cases in which he was able to perform a radical vulvectomy. BERVEN in Stage I cases, *i. e.* cases without clinical evidence of metastases, obtained a 5-year survical rate of 59.3 % and in Stage II cases, *i. e.* cases presenting clinical metastases but still operable, a 5-year survival rate of 32.9 %.

[1] Submitted for publication, June 9, 1947.

In order to consider the reasons for this disparity between the expected and the actual results of treatment, a series of 85 cases of vulval carcinoma seen and treated in Liverpool since 1931 is examined and reviewed in the present paper. As is inevitable in any series treated during the last twenty years, a period of necessary experiment and trial, the cases do not constitute a homogeneous group as regards the treatment adopted, the later cases treated when techniques were more standardised show better results than the earlier, but taken as a whole the series illustrates most of the ways in which radical treatment can fail.

The cases presented the usual features of this disease, its greater incidence in older women, the importance of leucoplakia as a precancerous lesion, the advanced state of the growths in many of the patients even at their first attendance. It was for instance possible to undertake radical treatment in only 61 cases out of the 85 and in 10 of these 61 the presence of clinical metastases rendered a cure unlikely. Three patients died as the result of the operation.

Briefly the results obtained in the 38 operable cases (Groups I & II BERVEN) treated 5 years or more ago by radical vulvectomy and radical adenectomy were as follows:

	No.	Alive 5 years or more without recurrence	Alive 5 years or more with recurrence	Total 5 years survival
Stage I	31	11 (35 %)	7	18 (58 %)
Stage II	7	0	1	1
	38	11 (29 %)	8	19 (50 %)

The main purpose of the present paper is to discuss the recurrences and not the aetiology of carcinoma vulvae, but it seems worth while to mention in passing an apparent relationship between the incidence of the disease and parity. This is set out in the following table.

Age group	No. of Patients	No. of Nulliparae	Ratio Nulliparous to Parous Women	% of Nulliparae
30—39	6	5	5 : 1	82 %
40—49	6	4	4 : 2	67 %
50—59	20	10	1 : 1	50 %
60—69	29	12	12 : 29	40 %
70—79	18	9	1 : 1	50 %
80—89	5	1	1 : 4	20 %

If the patients are divided into two groups, those under and those over 55 years of age, of the 24 patients aged 55 years and under, 1 or

6[illegible] % were nulliparae, of the 61 patients over 55 years of age, 22 or 3[illegible] % were nulliparae.

A larger series might not substantiate these proportions, but as they st[illegible]nd they seem to show that pregnancy may have a protective effect a[illegible]inst the development of cancer of the vulva, and if so that this pro-t[illegible]tion gradually wanes and is gone by the time the menopause is fully e[illegible]ablished.

In contrast to W. G. COSBIE's (4) findings in Toronto, that the disease is commoner in women in poor circumstances, no such difference was n[illegible]ted in this series, the social incidence of the disease being quite in-di[illegible]criminate, just as in the case of carcinoma corporis and in marked co[illegible]ntrast to the incidence of carcinoma cervicis, which in the north of England is very largely a disease of poorer women.

Recurrences after Radical Treatment

The recurrences fall into two groups, early recurrences occurring within two years of radical treatment, late recurrences occurring after two years. Such a division may seem somewhat arbitrary, but is has this justification, that many if not most of the recurrences appearing after two years seem to differ in origin and to a lesser extent in behaviour from the earlier recurrences.

Early Recurrences and their Prevention

The early recurrences fall into three groups, remote, inguinal and vulval and these may be considered separately:

1. *Early Remote Recurrences*

This group comprises those recurrences which develop outside the local cancer field, in the iliac glands or in some distant organ. They call for little or no comment except that almost invariably they show themselves within a few months of the radical treatment. Once a vulval cancer spreads outside the local or primary field it loses its slow growing character. The appearance of a remote metastasis without an initial local recurrence means the radical treatment was done too late. In a true Stage I or II growth it is almost an invariable rule that if an early recurrence develops, it will appear in the primary field, *i. e.* within the groins or vulva.

2. *Early Inguinal Recurrences and their Prophylaxis*

Inguinal recurrences are uncommon provided that the indications for the radical vulvectomy were sound and that the adenectomy was

complete. Their prophylaxis is clear, but while there is now no need to discuss in detail the technique of inguinal adenectomy it may not be amiss to discuss some of the experience gained in the present series.

The commonest site for these recurrences is the inner end of the inguinal scar. The chances of recurrence in this site can be minimised by careful dissection well to the inner side of the femoral vein, a dissection which bares the upper third of the pectineus muscle. To do this effectively needs a carefully planned incision. This is best made about ½" below the inguinal fold, bifurcating at its inner end, one branch passing sharply upwards over the pubic spine to meet the incision of the opposite side at the level of the upper border of the pubis, the other branch passing to the outer aspect of the vulva to form part of the vulvectomy incision.

If the glands are to be treated by irradiation alone, care must be taken to ensure that the boundary zone between the excised vulva and the lymphatic field receives a sufficient dosage.

While there appears to be general agreement, following the teaching of BLAIR BELL and TAUSSIG, that it is unwise to divide the inguinal ligament to remove the chain of glands along the external iliac artery and vein, there is no doubt that the dissection of Scarpa's triangle must be very thorough, and this means that the wounds heal badly, secondary disruption is likely to occur, and very possibly a patch of gangrene will appear at the edge of one of the flaps, particularly the lower. Drainage of the wound does not avoid this complication. TAUSSIG says »some degree of postoperative wound necrosis occurred in about 90 % of his cases». He ascribes this mainly to the age of the patients and their debility. In this series it did occur in some of the younger patients. Primary suture of the wounds is certainly an aggravating factor. The sequence of events is not surprising. In the first place it is impossible to keep the area dry and sterile because of drainage into it of lymph from the vulva, the anal canal and the legs. Secondly, a careful dissection of the deep inguinal glands from the inner side of the femoral vein entails dividing all the skin vessels supplying the flaps as they come off the femoral artery through the foramen ovalis of the fascia lata. Any added tension on the skin from approximation of the flaps will determine a necrosis, and because the lesion is primarily vascular rather than infective, chemotherapy is of little value to prevent this. This necrosis can be usually avoided and certainly always minimised by leaving the wounds unsutured, a method discussed in a previous paper. According to BERGEN (2), HYBBINETTE began to do this in Stockholm in 1934; more recently he has closed the granulating surfaces by Thiersch grafts. This practise seems unnecessary; the wounds will heal in any case by second intention in 6—7 weeks leaving a sound linear scar, and there is no doubt that

th convalescence with an unsutured wound is much less pyrexial and m re comfortable. Local chemotherapy is unsatisfactory and seemed to delay healing in the three cases in which I have tried it. This is not su prising in view of the mixed bacterial flora of these wounds. The iss e is important because there is no doubt that complications arising fr n the adenectomy wounds are responsible for much of the post-op rative mortality.

Secondary suture is sometimes worth a trial but the right moment to do it must be judged carefully or no gain will result. No time will be saved if it is deferred till the flaps are firmly anchored, on the other hand it must not be attempted before a collateral circulation is established. The tenth to the fourteenth day is usually the best time; in many cases the conditions never rise for its use.

There is one further point which is perhaps worth mentioning, the operation being one that is not done every day. It is best to operate first on the unaffected side. This will serve as a reminder of the niceties of the anatomy which will be valuable when the more heavily involved side comes to be done.

3. *Early Recurrences in the Vulva and their Prophylaxis*

Most of the early recurrences occur in the vulva itself. The most common sites are the vestibule, involving the urethral meatus, the lower vagina and the perineum. Usually these recurrences grow more rapidly than the original lesion but despite this their spread is mainly local. Both the adenectomy and the scarring of the first operation appear to have a blocking or restrictive effect on their spread. Despite this restriction they respond badly to treatment and their prophylaxis is of great importance.

Early return of growth in the vulva denotes nothing more than a failure to make the excision radical enough, but the problem of prophylaxis is not quite so simple as in the case of the groin, and some consideration must be given to the question of what constitutes radical treatment. In this context it may be worth while to discuss various factors which modify the spread of cancer in this site.

a. In the first place the lymphatic connections between the various parts of the vulva are so free that for the purpose of radical treatment the vulva must be regarded as one organ and not as a given area of skin.

b. Examination of any case of advanced leucoplakia will demonstrate the extent of the potential cancer field. Total leucoplakia occupies an area whose outer margins are formed by an elliptical line, in front commencing on the mons 1″ above the clitoris, passing backwards $^1/_2$″ lateral to the labia majora and terminating behind in the postanal cleft about

1″ posterior to the anus. Mesially the area is bounded by a line commencing in front close to the urethral meatus, passing backwards across the lateral vaginal wall about ½″ from its lower end and meeting its fellow on the posterior vaginal wall ½″ above the posterior commissure. The area bounded by these two concentric lines is the area which must be dealt with radically.

c. The recent studies of intraepidermal cancer have shown how foci of intraepidermal growth may be found scattered throughout the whole vulva, vide the papers by KNIGHT (6) and by JEFFCOATE, DAVIE and HARRISON (5). It is clear from these and other studies that leucoplakia, intraepidermal cancer and frank squamous cancer may coexist. Intraepidermal cancer or BOWEN's disease is not a cancer sui generis. In the present series there were five cases in which the typical red and sharply demarcated area characteristic of spreading intraepidermal cancer was found accompanying a squamous carcinoma. The so-called contact cancers which are so often seen accompanying a labial carcinoma are to be regarded not as implants or as metastases arising from lymphatic permeation from the primary growth, but as separate foci of intraepidermal cancer which have lit up and burst through the limiting basement membrane a little later than the primary growth.

All these points have a bearing on the rationale of a radical vulvectomy. The object is not the removal of a primary growth and the surrounding tissues, but the removal of the whole potential cancer site. This means that the excision must include the vestibule and the lower urethra, the lower vagina, and a wide area of perineal skin certainly as far back as the anus. Theoretically the postanal skin also should be removed, but postanal recurrences are so rare that it seems reasonable to make this much concession to the patient's comfort and stop short of the anterior anal margin. Such a risk should, however, never be taken if the perineal skin shows any precancerous lesion or the primary tumour occupies the posterior half of the vulva.

The wound resulting from so free an excision cannot be closed, but the operation must not be restricted to allow coaptation of the flaps at the expense of the object of the operation. All that can be done is to insert a few coaptative stitches where the tissues fall together naturally, usually at the anterior end of the wound, leaving the rest to heal by granulation.

No attempt should be made to refashion the urethral meatus. Such a step is unlikely to succeed, it will only further damage the soft mucous membrane and may be followed by a troublesome urethral stricture. This indeed did occur in one of the earlier cases of the series. Fortunately leaving the urethra, and for that matter the whole wound unsutured, does not appear to have any adverse affects.

As radical an operation as this may mean a good deal of blood loss, and it is better to secure haemostasis step by step, with ligature or diathermy, as the operation proceeds. If haemostasis is left to the end after the vulva has been excised a good deal of blood may quietly be lost.

Late Recurrences and their Prophylaxis

The late recurrences always appear in the vulva itself, and like the early recurrences and for the same reasons their spread remains local in most instances. Death usually results from direct infiltration of the neighbouring tissues. They differ from the early recurrences in having a slower rate of growth, often slower indeed than that of the primary lesion.

As regards their frequency there is a difference of opinion among various workers. According to BERVEN (2) they are rare but in the present series they were not uncommon, as the following cases illustrate.

Case No. 3. Nullipara aet. 36. In 1934 radical vulvectomy, squamous carcinoma. In 1945 fissured ulcer of two years standing on edge of scar. Papilloma on perineum. Considerable degree of leucoplakia present. Sections of fissure and papilloma squamous carcinoma.

Case No. 5. Nullipara aet. 35. 1931 radical vulvectomy. Squamous carcinoma. 1934 nodule in vulval scar section showed intraepithelial cancer. 1936, 1940 and 1943 small malignant ulcers were excised. In 1947 there is no evidence of any further recurrence.

Case No. 10. 2 para aet. 61. Radical vulvectomy 1939. Squamous carcinoma. Vulval recurrence with adenopathy 1944.

Case No. 19. 1929 excision left labium and glands by the late Dr. J. E. GEMMELL. In 1944 excision of right labium and glands by Dr. A. A. GEMMELL. On both occasions sections showed squamous carcinoma. Local recurrence in vulva 3 years after the second operation.

Case No. 20. 8 para aet. 78. Radical vulvectomy 1938. Squamous carcinoma. Local recurrence excised 1944. Alive without recurrence 1946.

Case No. 34. 2 para aet. 54. Radium to early primary 1931, squamous carcinoma. Glands not touched. Secondary excision of vulva 7 months later. Local recurrence 1942. In 1947 still alive but with massive malignant ulcer involving vagina and perineum.

Case No. 71. 0 para aet. 55. Squamous carcinoma. Radical vulvectomy with gland dissection 1932. Recurrence in vestibule 1938.

Case No. 78. 2 para aet. 55. Squamous carcionma. Recurrence in vulval scar extending into vagina 7 years after a radical vulvectomy.

In considering the nature of these late recurrences they would appear to have three possible modes of origin.

Some may be due to inadequate initial removal of a very slowly growing tumour.

Some are to be regarded as due to late activation of foci of intraepidermal carcinoma left behind at the first operation, manifestly an incomplete excision.

Neither of these modes of origin accounts, however, for late recurrences after a completely radical operation, and there would seem to be reasonable evidence for the view that there is a third mode of origin, that they are fresh growths and not recurrences of the original tumour. BERVEN inclines to this opinion with his statement, »Dies ist besonders wichtig, da die Vulva Sitz der prekanzerösen, chronischen atrophischen Vulvitis ist und die chirurgischen Erfahrungen gezeigt haben, dass oft ein neues Karzinom auf einer eventuell züruckgebliebenen prekanzerösen Vulvaschleimhaut entsteht.» (2).

There is certainly much to be said for this view. Although the whole potential cancer area may have been removed at the first operation it is common for the new vulva to become resensitised to the onset of cancer. This is evidenced by the frequency with which patches of leucoplakia reappear after a vulvectomy, whether performed for carcinoma or leucoplakia. Again, the long interval which sometimes intervenes before the recurrence appears is consistent with such an origin. In one case in the series the sequence could be seen, Case No. 5, a nullipara aged 35.

Two years after a radical vulvectomy for a squamous carcinoma leucoplakia reappeared. As a result of the war she was lost sight of for four years and then presented herself with an early localised squamous carcinoma situated on the perineum in one of the patches of leucoplakia.

This view of the nature of some of the late recurrences has more than a theoretical significance, it means that a case of carcinoma vulvae can never be regarded as permanently cured, that a continued watch must be maintained for the re-appearance of the precancerous lesion and that all such lesions must be re-excised immediately they are detected.

SUMMARY

There are clinical grounds for dividing the recurrences of carcinoma vulvae after radical treatment into two groups, early and late, since the nature and behaviour of the two differs in some respects. Early recurrences are of three types, remote recurrences occurring outside the primary field, inguinal recurrences, vulval recurrences. The prevention of the latter two groups consists of a radical operation so planned that all the

po ntial areas of recurrence are excised. The technique of adenectomy is discussed and at ntion drawn to the value of leaving the wounds unsutured.

With regard to the technique of the vulvectomy itself the mode of spread of cancer is t is site is considered with special reference to the implications of the spread of leucopla ia and Bowen's disease. A radical treatment must deal with the vestibule, the urethr l meatus, the lower vagina and the perineum. The late recurrences are invariably vul al and tend to remain localised for a long period. If they develop after an adequate pri ary excision they are to be regarded as fresh growths rather than recurrences of the riginal tumour. Their prophylaxis is important: all recurrent precancerous lesions mu be excised as soon as they are detected.

ZUSAMMENFASSUNG

Es liegen klinische Gründe vor für eine Einteilung der Rezidive von Vulvakrebs nach radikaler Behandlung in zwei Gruppen: frühe und späte Rezidive, da die Natur und der Verlauf dieser beiden Gruppen sich in mancher Hinsicht unterscheiden. Die Frührezidive weisen drei Typen auf: entfernte Metastasen ausserhalb des primären Feldes, Rückfälle in der Leistenbeuge und solche in der Vulva. Die Vorbeugung der letzteren zwei Gruppen besteht in radikaler Operation, die so geplant wird, dass alle eventuellen Rückfallsgebiete ausgeschnitten werden. Die Technik der Drüsenentfernung wird besprochen und auf den Wert des Unvernähtlassens der Wunden aufmerksam gemacht. Was die Technik der eigentlichen Vulvektomie anbelangt, so wird die Verbreitungsweise des Krebses an dieser Stelle ganz besonders im Hinblick auf ihren Zusammenhang mit der Verbreitung der Leukoplakie und der Bowen-schen Krankheit erörtert. Die radikale Behandlung muss das Vestibulum, die Urethramündung, die untere Partie der Scheide und das Perineum mit einbegreifen. Die Spätrezidive sitzen unfehlbar in der Vulva und bleiben lange lokal. Wenn sie nach sachgemässer primärer Exzision zur Entwicklung kommen, sind sie eher als neue Geschwulstbildung aufzufassen, als als Rückfälle des ursprünglichen Tumors. Ihre Prophylaxe ist wichtig: alle wiederkehrenden präkanzerösen Schäden müssen sofort nach ihrer Entdeckung entfernt werden.

RÉSUMÉ

Il y a des raisons cliniques pour diviser en deux groupes les récidives de cancer de la vulve après traitement radical: le »précoce» et le »tardif», attendu que leur nature et leur comportement diffèrent à certains égards. Les récidives précoces sont de trois types: récidives éloignées, se produisant en dehors du champ initial, récidives inguinales, récidives vulvaires. La prévention dans les deux derniers consiste à recourir à une opération radicale, conçue de façon à exciser toutes les zones de récidive potentielle. Discussion portant sur la technique de l'extirpation des ganglions, en attirant l'attention sur l'utilité, de ne pas suturer la plaie. En ce qui concerne la technique de la vulvectomie elle-même, le mode d'extension du cancer dans cette région fait l'objet de considérations qui s'attachent spécialement au rôle parallèle de l'extension de la leucoplasie et de la maladie de Bowen. Un traitement radical doit s'occuper du vestibule, du méat uréthral, du vagin inférieur et du périnée. Les récidives tardives sont invariablement vulvaires et restent locales pendant une longue période. Si elles se développent après une excision primaire adéquate il faut y voir de nouvelles tumeurs plutôt que des récidives du néoplasme originel. Leur prophylaxie est importante: toutes les lésions précancéreuses récidivantes doivent être excisées dès leur découverte.

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FROM THE GYNECOLOGICAL (PROF. J. HEYMAN) AND GENERAL (PROF. E. BERVEN) DEPARTMENTS OF RADIUMHEMMET, STOCKHOLM

MYOGENIC SARCOMAS OF THE UTERUS WITH SKELETAL METASTASES[1]

Report of Cases

by

Bengt Sylvén

The rarity of bone metastasis in cases of uterine leiomyosarcomas warrants a report of one case recently treated and a brief compilation of the Radiumhemmet material of these sarcomas with regard to the frequency of skeletal metastases.

The first case was reported by MILLER and ROGERS in 1928 (metastasis to the hip with spontaneous fracture). DECIO described one case with metastasis to the humerus. ROBBINS reported two additional cases with spinal metastases verified by autopsy. A fifth case (metastasis to the femur) was reported by BROOKE and THOMASON, who also mentioned another case observed by BLACKMAN. Unfortunately, the two last-mentioned cases are somewhat doubtful; the first one may have been an extension of a pelvic recurrence to the femur, and in BLACKMAN's case the verification of uterine malignancy was missing. Thus, only the four first mentioned cases deserve full attention. Further reports have not been found. In comprehensive reviews the occurrence of this condition has not been mentioned (4, 5).

At Radiumhemmet uterine sarcomas are largely classified according to ROBERT MEYER, and the pathologists forward due reservations with regard to highly anaplastic types, which do not warrant a histogenetic diagnosis (8). Since 1916 our register contains 77 verified cases of interstitial and submucous leiomyosarcomas. A short account of this material is presented in Table 1. Doubtful cases and cases with incomplete follow-up records have been transferred to a separate group, mainly containing cases not accepted for radiological treatment. From the compilation is seen that skeletal metastases from uterine leiomyosarcomas are not as rare as previously thought.

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Table 1.

Interstitial and Submucous Uterine Leiomyosarcomas from the Gynecological Department at Radiumhemmet from 1916 to 1946.

Verified cases admitted to treatment:		Distribution of skeletal metastasis
Alive, free of symptoms	15	
Alive, with metastases and/or recurrences	4	Case No. I
Alive, incomplete follow-up	1	
	20	
Died from sarcomatosis	51	
Died from intercurrency	6	
	57	
Total number of verifed cases	77	
Percentage with skeletal metastases	1.3	
Cases not admitted:		
For various reasons not included	—	Case No. II and III

If we only pay attention to the group of verified cases admitted to treatment the percentage of cases with skeletal metastases is very small. But if we include the advanced cases which were not accepted for treatment, we will get about 3 per cent.

Report of Cases

Case I. A woman aged 65 had constant pain in the left axilla for 10 months before admission. In November 1946 a large elastic tumour, firmly fixed to the ribs was felt in this axilla.

The case record reveals the existence of a previous malignant tumour. In 1925 in her 44th year she suffered from menorrhagia. The examination in the Gynecological service in 1927 including biopsy, indicated the presence of a large, partly cystic mural uterine leiomyosarcoma. The microscopic picture was very characteristic. Supravaginal amputation of the uterus was performed and the operation specimen confirmed the previous diagnosis.

After the operation in 1927 the patient had been well and free from symptoms. A control examination in October 1946 indicated that she was free from pelvic recurrence.

She was examined in the General service (Nov. 46) and a large, probably cystic tumour growing around the fourth rib in the left axilla was found. The tumour was fist-sized, nodular and consisted of an external part in the axillar adipose tissue, a central part in the thoracic wall around the fourth rib, and an internal part bulging into the thoracic cavity (Fig. 1). The lateral part of the fourth rib was surrounded and eroded by the tumour and showed a large defect.

Aspiration biopsy indicated its cystic character. After roentgen treatment the tumour showed an insignificant decrease in size, and was thus considered radioresistant.

Careful clinical and roentgenological examination did not reveal any other tumours. Thus, we had to look upon this particular tumour either as a primary one in the thoracic wall, or a metastatic tumour from the uterine sarcoma, which had been removed 19 years before. The latter proved to be right.

The axillary tumour was radically removed by Dr. CRAFOORD at Sabbatsbergs Hospital February 1947, and its gross anatomy is seen in Fig. 2. On microscopical examination

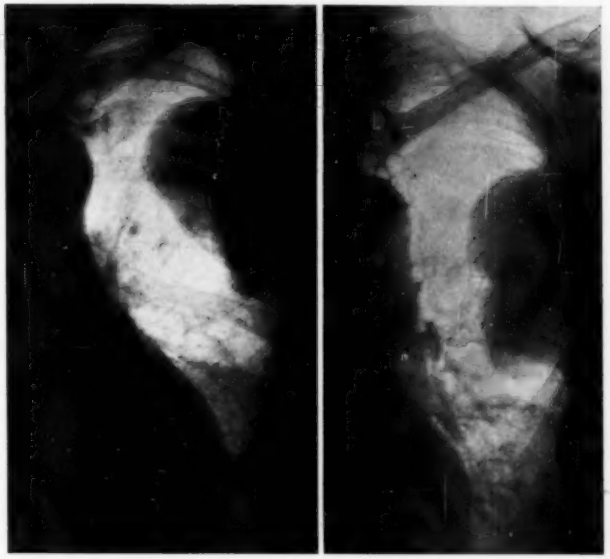

Fig. 1.

this tumour proved to have exactly the same structure as the previous sarcoma, including its cystic character. The woman withstood the operation well, and left the hospital free of symptoms.

Thus, we are justified in believing this to be a solitary metastasis from a previous leiomyosarcoma of the uterus, appearing 19 years after the removal of the primary growth. Judging from the large defect of the fourth rib corresponding to centre of tumour, the secondary growth originated in the rib.

Case II. A woman, 58 years old, was admitted to a country hospital with pain in and swelling of the right maxilla. A tumour was diagnosed and the patient was sent to Radiumhemmet, where she rapidly succumbed to generalised sarcomatosis. Post-mortem examination revealed a myometrical sarcoma of the uterus with metastases in most internal organs, including the thyroid, liver, right kidney, right maxilla and ninth thoracic vertebra. Judging from the autopsy record the primary sarcoma was of myogenic origin.

Fig. 2

Fig. 3

Case III. A woman aged 9, had for some months pain in and swelling of her right shoulder. A a country hospital, roentgen examinat on indicated a marked destruction and fracture of the right acromion and scapular spine. These parts of the sc p-ula were surgically removed, and the microscopic examination showed a polymorphous-cell sarcoma, proba ly metastatic in origin.

At Radiumhemmet, skin and pulmonary metastases were diagnosed together with a local recurrence in the operation scar. Gynecological exploration indicated a very large sarcomatous uterus. Re-examination of the microscopic slides suggested that the sarcoma was of myogenic origin. The clinical examination lends support to the view that it was of uterine origin. The patient could not be treated due to her bad condition, and she died after some days. Permission for post-mortem examination was not obtained.

Due emphasis should further be expressed with regard to the possibility that recurrences and remote metastases may also show secondary involvement of bone in cases of uterine sarcomas. Two typical cases with these characteristics are reported below.

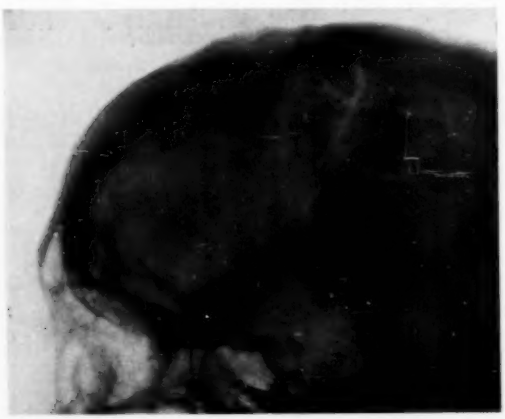

Fig. 4

F. A. Two years before admission to Radiumhemmet a woman aged 51, was operated in a country hospital for a uterine sarcoma. The microscopic diagnosis was »probably a myogenic sarcoma». One year after the operation a recurrence was diagnosed with a wide destruction of the right half of the sacral bone. The roentgenologists believed it to be a metastasis, but the clinical exploration indicated a large intrapelvic recurrence with secondary involvement of the sacrum. The case was too advanced to get radiological treatment.

K. K. O. A 52-years-old woman went to a country hospital because of profuse bleedings. A large myoma was subsequently enucleated. The pathologist found it to be a »malignant myoma». Radical operation was not possible because of technical difficulties. Two years later she observed a small hard tumour in her skull. During the following 18 months it grew to the size of an orange.

On admission the tumour measured 12 × 10 × 5 cm (Fig. 3). It was firmly fixed to the parietal bones but the overlying skin was freely movable. Roentgenologically the parietal bones showed destruction, so that only the inner table was left (Fig. 4). Bone spiculae were seen extending into the tumour. The lungs and lymph nodes were free of metastases. The gynecologists diagnosed a large pelvic recurrence. Fairly large roentgen doses were administered to the skull metastasis, but it proved to be radioresistant. Aspiration biopsy completely verified the suspicion of a new-growth from the primary sarcoma, both tumours being of identical structure.

Thus, the skull tumour proved to be a remote metastasis, probably deposited between the galea and the parietal bones, and had subsequently infiltrated and destroyed the underlying bone.

SUMMARY

From the material of Radiumhemmet, Stockholm, three cases are reported with distant skeletal metastases from uterine leiomyosarcomas. The occurrence of secondary involvement and destruction of bone by the action of metastatic nodules is mentioned. This paper lends support to the assumption that bone metastases from uterine sarcomas are not as rare as has previously been suggested.

ZUSAMMENFASSUNG

Aus dem Material des Radiumhemmet, Stockholm, wird über drei Fälle von Fernmetastasen im Skelett von einem Leiomyosarkom der Gebärmutter berichtet. Das Vorkommen eines Übergreifens und einer sekundären Zerstörung der Knochen durch metastatische Knoten wird erwähnt. Diese Arbeit stützt die Auffassung, dass Skelettmetastasen nach Gebärmuttersarkomen nicht so selten vorkommen, wie bisher angenommen wurde.

RÉSUMÉ

Trois cas de léiomyosarcomes utérins suivis de métastases osseuses à distance ont été étudiés au Radiumhemmet, Stockholm, et sont rapportés ici. L'éventualité d'un empietement secondaire et d'une destruction de l'os sous l'influence de nodules métastatiques est mentionné. Cet article confirme donc la supposition que les métastases squelettiques des sarcomes utérins ne sont pas si rares que l'ont prétendu de précédents auteurs.

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FROM THE ROENTGEN CLINIC OF THE MUNICIPAL HOSPITAL, AARHUS, DENMARK, AND THE RADIUM CENTER FOR JUTLAND (CHIEF: PROF. CARL KREBS, M. D.)

RESULTS OF ROENTGEN TREATMENT IN CHRONIC MYELOGENOUS LEUKOSIS[1]

by

Carl Krebs and *Jørgen Bichel*

When one has several times seen how irradiation therapy has been the means of markedly improving apparently hopeless cases of chronic myelogenous leukosis and even in some cases bringing about temporary restitution with complete disappearance of all, both subjective and objective symptoms, it is difficult to reconcile with those experiences the oft repeated assertion that irradiation, though excellent as a palliative measure, is incapable of prolonging the life of the patients. For of course there is no doubt that the irradiation treatment in some cases is directly lifesaving.

As we at the Radium Center in Aarhus during a number of years have given particular attention and much time to the examination and control of leukosis patients, it may perhaps be of interest to see what the results have been. In the last fifteen years, up to May 1946, we have treated, in all, 222 patients with various forms of leukosis. Of these, 58 were chronic myelogenous, 129 chronic lymphatic, 22 acute, the remaining 13 more uncommon forms or of less certain diagnosis. Since it is especially in the myelogenous leukoses that the results of the irradiation treatment are outstanding, and as, moreover, this type is more readily definable from other, closely related affections than the lymphatic forms, we have for the present confined our analysis to the results in these, and particularly in the chronic.

It is usually said that there are even transitions from the acute myelogenous leukoses to the chronic forms, and that the delimitation between the two therefore becomes more or less a matter of chance. This is undoubtedly true if we take only the duration of the disease as criterium. It is possible that the process is essentially the same in the two forms (a question which we shall not discuss here), but most of the investiga-

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tors who have had to do with human leukoses will probably admit tha as regards the myelogenous the diagnosis between acute and chroni seldom gives rise to doubt. The clinical picture of the typical acute mye logenous leukosis is so different from that observed in the chronic form — and so is the hematologic, which likewise, with its overwhelmin preponderance, right from the beginning, of »blasts» without any ten dency to differentiation, both in the blood and in the hematopoieti organs, absolutely differs from that of the chronic — that there is hardly ever any difficulty about the correct rubrication. Both clinically and hematologically it is surprisingly rare to find intermediate forms. It is well known that in the terminal stages the two forms may in both respects approach each other, but there the previous course as well as the objective findings, with the often considerable enlargement of the spleen in the chronic cases, as a rule makes the diagnosis easy. If we rubricate on this basis (as we have been doing in Aarhus) it must be admitted that the duration of the chronic leukosis in some cases, if only a few, can be shorter than it is possible with an acute form of the disease, and that the terms acute and chronic are, consequently, to a certain extent misleading. But as they are the ones generally used, and are probably often more or less consciously used according to the same principles, we have kept to them.

A difficulty for the evaluation of the results of the irradiation treatment is the lack of control material. The fact that nowadays nearly all patients with chronic myelogenous leukosis are treated with roentgen makes it impossible to get any material of non-irradiated, much less of untreated, cases for comparison. An analysis of 52 non-irradiated cases, published by MINOT, BUCKMAN and ISAACS in 1924, is often made to serve for this purpose, but it has, of course, to be used with some reservation, since many different factors — geographic, socio-economic, of race and of time — have an influence on the composition of such a material and on the course of the disease. In that respect it is sufficient to point to the difference in the numerical proportion between lymphogenous and myelogenous leukoses in the various materials and to the difference in the ages of the patients at the onset of the disease. The last-named factor is important because patients advanced in years will have a shorter duration of life simply on account of their age. Besides, it must be remembered that the material compiled by MINOT, BUCKMAN & ISAACS did not consist of non-treated cases, but only of non-irradiated.

The greatest difficulty in obtaining a statistical material for evaluation of the duration of life of leukosis patients is the impossibility of determining with absolute certainty the time at which the disease has set in. There is here hardly any other way than through a careful anamnesis to find out when the first subjective or objective symptoms unquestionably

re rable to leukosis made their appearance. An estimate on this basis, ho ever, will undoubtedly result in the past duration of the disease be g found much shorter than what it has actually been. It is by no means uncommon quite incidentally to find that a patient who co es to examination for an entirely different disease is also suffering fro leukosis.

With all these reservations in mind it is rather curious to see how clo ly the survival curves in the different collective statistics approach eac other, and how nearly they coincide with MINOT, BUCKMAN & ISA CS's curves for non-irradiated, from 1924.

At the Radium Center in Aarhus, all patients with chronic myelogenous leukosis, except one, have been treated with roentgen. The principal indication for the irradiation has been that the patient felt ill, while patients without any subjective symptoms have not been irradiated, no matter how high the leukocyte count or how large their spleen. The subjective symptoms of which there chiefly is question are partly the fatigue and the troubles referable to the anemia, partly the local troubles referable to the enlarged spleen. In the last years, the irradiation has been given over one or severals fields of 10 × 10 cm. from in front to the spleen, daily or every second day; but until we are sure about the patient's individual reactions only small doses, often no more than 25 r every second day (160 kv., 4 ma., through 1 mm. Cu. + 1 mm. Al.; distance 40 cm.) are given.

While it is the patient's subjective symptoms which furnish the indication for the irradiation treatment, it is fully as much, or more, the hematologic findings which are determining for its discontinuation. In practically all cases it is discontinued long before the symptoms have fully disappeared. If the treatment has been successful, it is interrupted when the leukocyte count has fallen to about one-third of the initial figure — though by preference not to below 50,000 per cubic millimeter — somewhat depending on how rapid the fall has been. In cases of the aleukemic type, where there is no increase of the leukocyte count, the treatment is discontinued when the standard metabolism approaches the normal values. If there is no rise in the hemoglobin per cent and the erythrocyte count, and especially if there is a fall in these values, the treatment is interrupted and an antianemic therapy, oftenest in the form of blood transfusion, is tried, in order to get the patient into a condition where treatment can be resumed. Also if the differential hematologic picture during the treatment shows increased displacement toward the left, we stop; while even a rather high »blast» per cent at the beginning of the treatment is no contraindication. The thrombocyte figures seldom present any difficulty. In the first place they are in chronic myelogenous leuko is seldom lowered, but on the contrary often increased; and if

they *are* somewhat lowered, they usually rise during the treatment. Considerable rises of temperature, which incidentally are seldomer in myelogenous than in lymphogenous leukoses, will oftenest only call for a reduction of the dose. If the patient's condition is fairly good, a few days' hospitalisation will suffice, whereupon he can continue the treatment as out-door patient.

Besides these simple examinations — determination of the standard metabolism and the so-called »complete blood examination» — which are made twice a week during the treatment, we have made various biochemical tests, chiefly of scientific interest, none of which seem, however, to have yielded better guidance for the treatment than the two simple ones named. It may be added that we have made it a special point always to have the weekly blood examinations as well as the clinical and therapeutic follow-up of the individual cases done by the same person.

Of the 58 patients with chronic myelogenous leukosis treated at the Radium Center, 10 were alive at the end of the period covered by the present study (May, 1946), 1 had died without having received roentgen treatment, and in the case of 3 the anamnestic data are incomplete. The ages of the 55 at the onset of the disease were as follows:

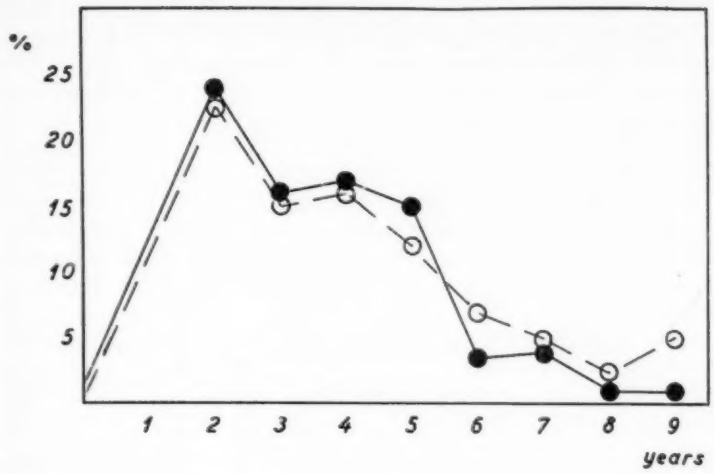
Age	Male	Female	Total	Per Cent
0— 9	0	1	1	2
10—19	2	1	3	5
20—29	3	2	5	9
30—39	5	6	11	20
40—49	5	8	13	24
50—59	10	5	15	27
60—69	2	3	5	9
70—79	0	2	2	4
	27	*28*	*55*	*100*

It seems that our material contains a higher percentage of elderly patients than the materials from most other places. In most of the other statistics published — for instance in those of MINOT, BUCKMAN and ISAACS, and of WARD, HOFFMAN and CRAVER — the highest percentage is in the age group 30—40.

The average duration of life after the onset of the disease for the 44 roentgen-treated (23 males and 21 females) was 40.7 months (39.1 months for the males, 41.5 for the females).

The following chart shows the incidence (per 100 cases) of duration of life of our 44 patients and of the 52 patients from MINOT, BUCKMAN & ISAACS's report who did not receive irradiation treatment (solid line).

As the two curves show, there is no essential difference, as regards the duration of life of the patients, between our irradiated material and



MINOT, BUCKMAN and ISAACS's non-irradiated; and the same applies, in fact, to all the published materials that have been analysed in this manner and where the same method of statistical comparison has been used (WARD, HOFFMAN and CRAVER, ARNDT and GLOOR, KLEWITZ and SCHUSTER).[1]

MINOT, BUCKMAN and ISAACS have tried to determine for how many months after the institution of the treatment the irradiated patients have remained »efficient», and have compared this with the length of time the non-irradiated have remained so after the time when an irradiation treatment might have been commenced. The result of this comparison clearly shows the enormous value of the irradiation therapy. For while the irradiated do not live very much longer than the non-irradiated, they enjoy during their remaining years a relative measure of well-being and capacity for work, in contrast to the non-irradiated, whose existence will always continue to be miserable. Of their 52 non-irradiated cases, there was only spontaneous remission in 7.7 per cent.

If we survey the by now considerable literature on irradiation therapy in leukosis, we find that most of the authors think that this therapy in a

[1] The average duration of life is given by various authors as follows: KLEWITZ & SCHUSTER (26 patients) 31 months and 20 days; HOFFMAN & CRAVER (71 patients, with omission of 4 who lived exceptionally long) 3.27 years for females, 3.4 years for males; MCALPIN (24 patients) 3 years; PASCUCCI, 2.5 years; MINOT, BUCKMAN & ISAACS (78 patients) 3.4 years, and for non-irradiated (52 patients) 3.04 years; ARNDT & GLOOR (39 patients) 4.1 years; LEUCUTIA (18 patients) 3.3 years; LEAVEL (87 patients) 3.2 years; WESTROBE & HASENBUSH, 2.79 years.

number of cases can be directly lifesaving. The irradiation must therefore have been the means of prolonging the life of such patients. But apart from this it is also difficult to understand, on general principles, that it should not be possible to prolong the life of the patients, considering that the irradiation improves their general condition and thus makes them better able to resist intercurrent affections. That this does not find expression in a longer duration of life statistically, may be due to a variety of causes. In the first place it must again be remembered that the non-irradiated patients used as material for comparison were treated in a different way, and therefore perhaps lived longer than the non-treated. (As we know, arsenic has a marked effect in myelogenous leukosis.) Further it is possible that the excursions are too few and too slight to affect the statistical results. And finally it is possible that the irradiation treatment in certain cases shortens the life of the patient, while in others it prolongs it. That this is so, is not improbable. The authors on leukosis therapy time and again warn against overdosing, and just as often stress the necessity of adapting the dosage to the individual case, because the sensitivity and tolerance varies immensely from one patient to another. It is difficult to determine in the individual case whether the lethal issue has been hastened by a too intensive irradiation therapy, but there are examples enough which might indicate that such has been the case.

Very often the leucocyte count is used as guide for the treatment, and most authors advise that the irradiation should be discontinued when the figure gets down to about 20,000 per cubic millimeter, in order to avoid the development of granulocytopenia with possible transition to blastoleukosis. It is realised that the fall in the leukocyte count continues for some time after the irradiation has been suspended, but it is doubtful if it is always known for how long this is the case. As an example of how long such an »after-effect» may last, we give the following case of a patient who was treated with roentgen from Nov. 17th to Dec. 2nd, 1937, total dose 400 r to the spleen. The schema shows the various hematologic changes, during and after the treatment, in this typical case of chronic myelogenous leukosis.

It will be seen that during the two weeks' treatment the leukocyte count fell from 298,000 to 91,200. At the after-examination three months later the patient turned up perfectly well, but with only 4,700 leukocytes and otherwise almost normal blood picture. This result may seem highly satisfactory; but it is not impossible that his leukocyte figure may have been still lower shortly before or after the time of this after-examination, and it is our opinion that he has really been overdosed. Other, similar examples might be given, and though we cannot prove it with certainty we therefore believe that in a number of cases the dosage has in spite of all caution been excessive.

	Nov. 17th, 37	Nov. 20th, 37	Nov. 26th, 37	Nov. 29th, 37	Dec. 2nd, 37	Mch. 1st, 38	June 5th, 38	Oct. 7th, 38	Feb. 14th, 39
Sedi[illegible]ntation mm/hour	20	22	22	22	22	10	6	8	2
Red [illegible]ells	2.94	2.67	2.67	2.76	3.14	4.77	4.10	4.38	4.30
Whit[illegible] »	298,800	231,800	176,300	156,800	91,200	4,684	5,930	9,400	19,700
Hem[illegible]obin, per Cent..	62	60	60	64	68	89	91	93	98
Plate[illegible]s	> 600,000					about 400,000			
Blast[illegible]	0.3			0.3	0	0		0	
Unrip[illegible] Myelocytes	0			0	0	0		0	
Half-r[illegible]e »	1.6			1	0.6	0		0	
Neutr[illegible]phile »	17.6			9.3	6.3	0		1	
Eosin[illegible]hile »	1			0	0	0		0	
Basophile »	0.3			0.3	0	0		0	
Metamyelocytes	15.3			13.3	12.6	0		3	
Neutrophile Leukocytes	61			71.6	71.6	64.3		78.5	
Eosinophile »	0.3			0.3		1.3		0.5	
Basophile »	2			2.3	4	2.6		1	
Lymphocytes	0.3			0.3	1.3	25.3		11	
Monocytes	0			1	2.3	6.3		5	

In order to find out what factors in the case of the individual patient play a rôle for the estimate with regard to the prognosis, we have tried to analyse the possible relation between the initial hemoglobin-, leukocyte- and sedimentation rate values, the absolute number of the most immature granulocytes (blasts + promyelocytes) together with the size of the spleen, and the remaining duration of the life of the patients. The values reckoned with are those found at the examination made when the patient was first referred to us, and the duration of life the length of survival from the same date. The many diagrams would take up too much space, therefore we will only say that the result of these investigations has been that even within very wide limits it is practically impossible on the basis of those factors, as revealed at the initial examination, to prognosticate anything with regard to the individual case. Even a relatively high number of very immature granulocytes in various stages of development need not mean a worse prognosis, which also accords with the fact that it is no contraindication to the institution of a treatment. A fairly safe basis for prognosis in the individual case it seems that one can only get after having seen the reaction to the first part of the roentgen treatment.

SUMMARY

[illegible]he possibilities of judging the efficacy of roentgen therapy in the treatment of leuk[illegible]is is examined especially with regard to the influence of roentgen therapy on the dura[illegible]on of the patient's life. The difficulties in judging is pointed out. The material is com[illegible]red with MINOT, BUCKMAN and ISAAC's statistics of patients with leukosis who

have not been treated by rays. The results are remarkably similar. Although, in certain cases, the life of individual leukosis patients is actually prolonged by roentgen therapy, one may suppose that in others, despite the favourable initial effect, it only hastens the beginning of the terminal phaze.

ZUSAMMENFASSUNG

Es werden die Möglichkeiten zur Beurteilung der Effektivität der Röntgentherapie in der Leukosebehandlung untersucht, besonders der Einfluss der Röntgenbehandlung auf die Lebensdauer der Leukosekranken. Es wird auf die Schwierigkeiten bei der Beurteilung hingewiesen. Das Material wird mit der Statistik von MINOT, BUCKMAN und ISAACS über nicht-strahlenbehandelte Leukosepatienten verglichen. Die Ergebnisse decken sich auffallend. Während die Lebensdauer einzelner Leukosepatienten durch die Strahlenbehandlung zweifelsohne wirklich verlängert wird, muss man annehmen, dass in anderen Fällen, trotz guter Initialwirkung, das Eintreten des Endstadiums beschleunigt wird.

RÉSUMÉ

L'auteur examine les possibilités d'apprécier l'efficacité de la radiothérapie dans la leucémie, et en particulier son influence sur la durée de la vie des malades atteints de cette affection. Il souligne la difficulté de porter un jugement. Le matériel est comparé à la statistique de MINOT, BUCKMAN et ISAACS concernant des sujets leucémiques non traités par les Rayons. Les résultats concordent avec une exactitude frappante. Etant donné que sans nul doute, dans certains cas, on prolonge la vie de quelques leucémiques par la radiothérapie on doit supposer que chez d'autres, en dépit d'un effet initial favorable, on hâte l'apparition du stade terminal.

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FROM RADIUMHEMMET, STOCKHOLM (CHIEF: PROF. E. BERVEN)

TWO CASES OF CYSTIC LYMPHANGIOMA OF THE NECK WITH MEDIASTINAL INVOLVEMENT[1]

by

Folke Jacobsson

Cystic lymphangiomas are rare tumours, usually met with on the neck, and, according to HYATT (quoted by MAC GUIRE), only 107 cases with this localization had been published up to 1932. Among these, cases of other cysts of the neck will probably have been included. Cases with mediastinal involvement seem to be very rare, according to the literature. Such cases have been reported by FIGI, GOETSCH, HANSEN, LEMON, LYLE, MARTIN & LELONG, MICHAELIS, PORTMANN, SCHMIDT and SINGLETON. Two cases have been admitted for treatment at Radiumhemmet.

Histologically cystic lymphangiomas are benign tumours.

MOORE gives the following histological description: »The tumours consist of numerous small and large, thin-walled cysts, filled with a clear straw-coloured or colourless fluid. Some of the cysts may communicate with one another, but most of them are independent, closed cavities. Between the cysts there is a small amount of fibrous tissue, in which the normal structures of that region are compressed and atrophic. In the walls of the cyst and in the connective tissue there are small masses of lymphoid tissue.

Microscopically the cysts are seen to be lined with a flattened endothelium, which rests upon a moderately collagenous connective tissue. About the edges of many cysts there are small, solid or hollow evaginations, which extend into the surrounding tissue. Mitotic figures are rare. Skeletal muscle fibres and other structures trapped between the cysts show advanced atrophy. Chemical examination of the fluid shows it to contain only a small amount of protein, but a large amount of cholesterol. Study of the sediment in the fluid shows desquamated endothelium and a few white and red blood cells.«

According to SABIN (quoted by MOORE), the lymphatic vessels first

[1] Submitted for publication, May 16, 1947.

appear as outgrowths from the primitive jugular bulbs or from the great veins in the region of the groin. These evaginations lose their connection with the primitive venous system and later on, after many lymph-vessels have developed, a secondary connection with the jugular vein is established (Fig. 1.)

In view of the fact that cystic lymphangiomas are situated almost exclusively in the region of the neck or of the groin, it is considered highly probable that these tumours originate from some anomaly in the development of the primitive lymphatic spaces (MOORE, SINGLETON et al.).

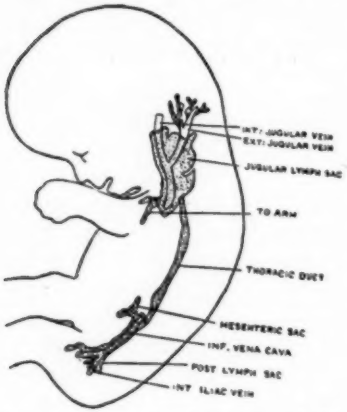

Fig. 1. The development of the primitive lymphatic spaces (reproduction from A. SINGLETON).

Cystic lymphangioma of the neck is usually obvious at birth or emerges during the first years of life. But it may also appear much later. GOETSCH has reported two cases in which the tumour appeared at the ages of 34 and 38 years respectively. The growth is usually slow, but periodically it is faster. Variations in the size of the tumour are common, usually owing to infection. Data as to sexual frequency are spare. Of the 29 cases, reported with such data by FIGI, GOETSCH and SINGLETON 9 were male and 20 female. At Radiumhemmet of 4 cases 3 were male and 1 was female.

The tumours are localized on the right or left side or in the median line of the neck, or they occur on both sides. In DOWD's summary of cases from the literature the localization is given in 73 cases out of 91, the tumour occurring on the right side in 33 cases, on the left in 26, and on both sides in 14 cases. Of FIGI's, GOETSCH's and SINGLETON's total of 29 cases with data as to the localization 14 were situated on the right, 10 on the left, 4 on both sides, and 1 in the median line of the neck.

As regards cases with mediastinal involvement, data as to sex and localization are scanty. Of 5 cases 1 was male and 4 female. 2 tumours were situated on the right and 3 on the left side of the neck. In both of the author's cases the patients were male, and the tumour on the left side.

The cystic lymphangioma of the neck is lobulated, is rather poorly deliminated, and varies greatly in size. The cervical portion may be as large as the head of a child. Extension from the temporal region to the hilus of the lung is described. The tumour is soft and fluctuating in parts and in parts firm, and in typical cases not compressible. It has a peculiar

and rather characteristic rubbery or spongy consistency on palpation. The tumour originates beneath the deep cervical fascia on the lateral side of the large blood vessels and in front of the spinal nerves. It may extend into the subcutaneous tissues, into the thorax or the axilla. Usually the tumour is not movable over the underlying structures, because it penetrates into the surrounding tissues, with branches between the blood vessels and nerves. The overlying skin is usually of normal appearance, although it may be tense or stretched owing to the large size of the tumour. The size and extension of the intrathoracic portion vary greatly. In a case related by HANSEN the tumour took up the greater part of the thorax. The patient, aged 1 month, died of suffocation caused by the tumour. MICHAELIS described a case where the intrathoracic portion of the tumour consisted of one portion in the left half of the thorax, as big as a duck's egg, and another portion in the anterior part of the mediastinum.

Occasionally the cysts cause compression of the trachea, with consequent dyspnea, and of the oesophagus, with dysphagia. Pressure on the blood vessels and nerves sometimes results in hyperesthesia and paresthesia.

Secondary infection of the tumour cysts is a not uncommon complication, either as a result of a respiratory infection or of an attempt at surgical removal of the tumour. In some cases the infection destroys the endothelial lining, and the cysts undergo regression (MOORE).

The diagnosis of cystic lymphangioma is not difficult. The history is often helpful for the diagnosis. Of other cystic tumours of the neck, cysts of the thyroglossal duct occur in the anterior median line of the neck, usually associated with a palpable subcutaneous cord, attaching the cyst to the hyoid bone. These cysts are comparatively small, and as a rule they are tense. Branchial cysts are always unilocular, well delimited and usually smaller and more tense than the cystic lymphangioma. Lipomas may be difficult to differentiate, although their firmer consistency and less diffuse outline will as a rule distinguish them. Dermoid cysts have a distinctly doughy consistency on palpation. Unlike the haemangioma, the cystic lymphangioma is as a rule not compressible.

The diagnosis of the intrathoracic portion ought not to be difficult, in view of the history, the age of the patient and the presence of a cervical portion. Repeated roentgen examinations will confirm the diagnosis.

The tumour ought to be surgically removed, if that is possible. The surgeon, however, is often startled by the deep extension of the tumour and the difficulty of loosening it, with all its branches between the blood vessels and nerves. It is therefore often impossible to remove the whole tumour, and there is a risk of recurrence. If the tumour only extends

slightly into the thorax, it is possible also to remove its intrathoracic portion. To remove considerable intrathoracic portions is, however, considered very difficult.

There is always a rather serious risk of infection in connection with the operation. In DOWD's summary of 91 cases (1913), nearly all had been operated upon, and in about 42 % of the cases the issue was fatal. In 1938 GOETSCH had operated 9 cases with a fatal outcome in 1 case, and SINGLETON 1937 had operated 8 cases with a fatal result in 1 case. There are also some accounts of operations on cystic lymphangiomas of the neck with mediastinal involvement. One case was operated on by LYLE 1914, with success. The intrathoracic portion had an extension behind the sternum of about 5 cm. A similar case was operated on by DOWD with a fatal outcome. Another case was operated on in 1933 by MARTIN & LELONG, with primary good result. MICHAELIS had a fatal result in a case operated upon in 1934. PORTMANN describes (1945) a girl of 10 months of age with a tumour with extensive mediastinal involvement. She died on operation from uncontrollable haemorrhage. SINGLETON made a partial removal of the tumour in two cases. In one case there was a fatal result, caused by infection 10 months after the operation. The other case was treated with roentgen postoperatively and was free from symptoms 16 months after the operation.

Some authors have tried radium- and roentgen treatment. 1928 FIGI had treated 12 cases with radium at a distance of 2.5 cm. The treatments were repeated at intervals of 2—3 months. In 4 cases the roentgenogram showed evidence of extension of the tumour into the thoracic cavity. The intrathoracic portion was not treated In 6 cases there was a fatal outcome, thought to be due to infection during the course of the treatment, and only 3 cases were free from signs and symptoms. Only primary results are given. FIGI does not distinguish between tumours with or without mediastinal involvement when reporting his results. In one case, with an intrathoracic portion, the cervical portion was treated for 2 years. There was a considerable shrinkage of the cervical portion, but then the patient got a whooping-cough, and the tumour quickly regained its former size. FIGI believed that the enlargement of the cervical portion was due to infection from the intrathoracic portion of the tumour. GOETSCH and SINGLETON have each given roentgen treatment to a partly operated case, with success. In GOETSCH's case part of the tumour was intrathoracic and the cervical portion was surgically removed. No definite information as to the dosage was given. There was a considerable reduction of the tumour. In PORTMANN's case, later operated upon with a fatal outcome, the patient was given a trial of roentgen therapy, and the cervical masses began to diminish in size.

Fig. 2 a. Fig. 2 b.

Fig. 2 a. The first patient on admission (the lines on the skin indicate the treatment field).

Fig. 2 b. The same patient 3 1/3 years later.

The two cases treated at Radiumhemmet are presented below.

Case I. Patient E. M. I. J. Record No. 14414/1942. A boy, 14 months of age when first admitted to Radiumhemmet in 1942.

Since birth the patient had had a tumour in the left side of the neck. The parents had not noticed any growth of the tumour. Otherwise the patient was healthy.

About 14 days before admission to Radiumhemmet the patient was examined at a county hospital. A tumour was found on the left side of the neck, about the size of a man's fist. A roentgen examination revealed a shadow in the left upper part of the thorax, interpreted as being due to an intrathoracic portion of the tumour.

A biopsy specimen was taken from the cervical portion of the tumour. At this operation, it was found that the tumour consisted of rather thick-walled cysts about the size of a walnut, filled with colourless fluid. The cysts were securely fixed to the surrounding tissues, and it was difficult to remove them. The tumour was considered inoperable.

The pathological examination of the biopsy specimen showed cystic lymphangioma.

The patient was then sent to Radiumhemmet for treatment.

Status on the 13th of November, 1942: General condition unaffected. No dyspnea or cyanosis. The patient had a slight hacking cough.

The tumour in the left side of the neck was soft and of about the size of a man's fist. It bulged laterally and formed a hump on the neck (Fig. 2 a). It extended from the lobe of the ear to down beneath the clavicle. The tumour was freely movable against the clavicle, and it was easy to put one's fingers under the lateral part of the tumour. Medially

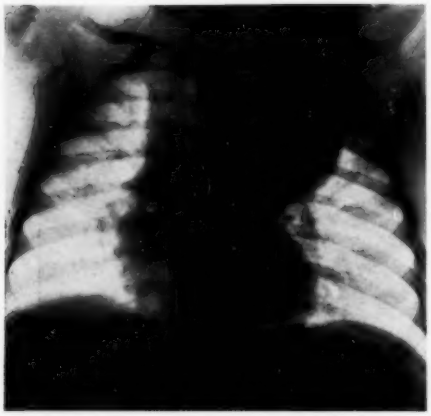

Fig. 3 a. The intrathoracic portion of the tumour of the first patient on admission.

it was fixed to the deep tissues. The tumour was not compressible and consisted for the most part of several large cysts.

The shadow in the left upper part extended slightly beneath the hilus of the lung. Upwards the shadow fused with the soft parts of the neck. The shadow appeared largely in the anterior part of the thorax and was about 5.5 × 7 cm in size. The trachea was considerably dislocated to the right but was only slightly compressed. (Fig. 3 a.)

Roentgen treatment was given (both to the cervical and the intrathoracic portion of the tumour) from an anterior and a posterior field, each 10 × 15 cm. The patient received 1,000 r with back-scatter per field. The treatment was given daily on one field with a dose of 200 r. The irradiation factors were 160 kv, 15 ma, 50 cm FS-distance and $^1/_2$ mm Cu + 1 mm Al.

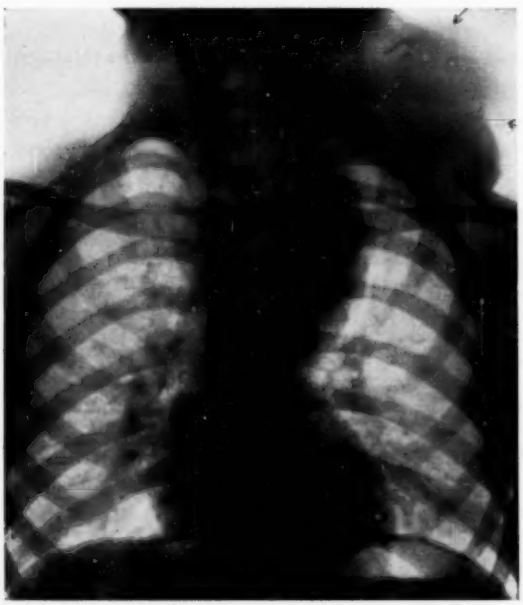

Fig. 3 b. The tumour 3 $^1/_2$ years later with calcifications in the cervical portion.

About 3 months after the treatment there was no certain change in the size of the tumour.

7 months after the treatment the cervical portion of the tumour was slightly reduced, but the intrathoracic portion seemed unaffected.

There was further regress of the cervical portion about 1 $^1/_2$ year after the treatment, and also a regress of the intrathoracic portion. The tumour was still inoperable and a new series of roentgen treatments was given. The patient received 200 r × 2 on each field with the same irradiation factors as in the first series. The boy was again controlled 3 years and 4 months after the first examination. He was in excellent condition and had grown normally for his age. There was a slight further regress of both the cervical (fig. 2 b) and the intrathoracic (fig. 3 b) part of the tumour. The roentgenogram

Fig. 4 a.

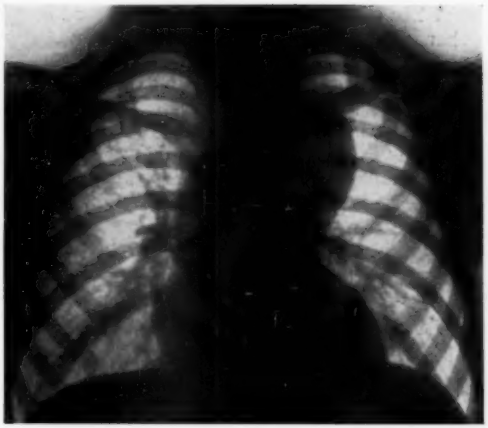

Fig. 4 b.

Fig. 4 a. The intrathoracic portion of the tumour of the second patient on admission.
Fig. 4 b. The same tumour nearly 3 years later.

also exhibited calcifications in the cervical portion (fig. 3 b). A new series of roentgen treatments was given to the cervical portion. It received in all 300 r × 3 with treatment alternately to the anterior and posterior field. The surrounding tissues were carefully shielded with lead. Otherwise the irradiation conditions were as in the first series.

Case 2. Patient L. G. J. Record No. 311/1943. A boy, 10 months of age when first admitted to Radiumhemmet in 1943.

Since birth the patient had had a tumour on the left side of the neck. To begin with the tumour was rather soft, but with increasing size it got firmer. The parents were worried, because it seemed to them that there was a wheeze in the patient's chest during breathing, and therefore they had the boy examined at a county hospital 2 months before his admission to Radiumhemmet.

At the county hospital it was found that the patient had a tumour in the left side of the neck, about the size of a hen's egg, with the main part cystic. The general condition was unaffected.

The tumour was operated on, and it was found to be multilocular and cystic and extended medially to the trunk of the large blood vessels, and there were also branches between the large vessels. Some cysts were situated so far down in the thorax that the surgeon would not take the risk of removing them. During the removal of the tumour the jugular vein was partly damaged. The patient stood the operation well.

The pathological report on the examination of a specimen of the tumour was cystic lymphangioma.

About a week after the operation, the wound was infected and the patient showed a rise of temperature. A roentgen examination of the chest revealed a shadow in the left upper, anterior part of the thorax. The extension of the shadow was about the size of a tangerine. There was a displacement of the trachea to the right and backwards (Fig. 4 a).

The shadow was believed to be caused by pneumonia. There was, however, no great change of the shadow during the following 14 days and so it was thought that the shadow was caused by a mediastinal tumour.

The patient was then sent to Radiumhemmet for treatment.

Status on the 7th of January 1943: General condition unaffected. No fever. No dyspnea or cough.

On the left side of the neck there was a scar and underneath it a slight thickening of the tissues. Above the scar the tissues were slightly swollen.

The intrathoracic shadow was now diagnosed as an intrathoracic portion of the lymphangioma.

Roentgen treatment was given from an anterior and a posterior field each about 100 cm^2, both to the swollen parts of the neck and to the intrathoracic portion of the tumour. The patient received 1,400 r with backscatter per field. The treatment was given daily on one field with a dose of 200 r. The irradiation factors were 170 kv, 15 ma, 50 cm FS-distance and $^1/_2$ mm Cu + 1 mm Al.

On examination 4 months after the treatment, there was no tumour to palpate in the neck. The intrathoracic portion had slightly diminished.

The next examination at Radiumhemmet was about $1^1/_2$ years after the treatment. No tumour was palpated in the neck. The intrathoracic portion was unchanged. The patient was in excellent condition and a second series of roentgen treatments was given to the intrathoracic portion of the tumour from an anterior and a posterior field. The patient received 250 r $\times$ 2 per field, and the irradiation factors were the same as in the first series. There was no change in the status 1 month after the second series of treatments.

The boy was again examined at Radiumhemmet nearly 3 years after the first series of treatment. He had been in good condition since the last follow up examination and had grown normally. There was no tumour in the neck and further regress of the intrathoracic portion was shown. (Fig. 4 b.)

In both the cases described there was a cystic lymphangioma of the neck on the left side with mediastinal involvement. The patients were boys and on admission they were 14 and 10 months old respectively. The tumours had been manifest since birth. The diagnosis was verified by biopsy specimens from the cervical portion of the tumours. In the second case, the cervical portion of the tumour was surgically removed, with good result. Otherwise the tumours had been considered inoperable. The tumours were treated with roentgen in series, with long intervals between the series and with rather small doses. The principles for the treatment will be discussed later. The result has so far been good, as in both cases the tumour has diminished in size, and there have been no complications. The patients are in excellent condition and have no inconvenience from their tumour. The follow up of the cases is being continued.

In the treatment of cystic lymphangiomas of the neck with mediastinal involvement, operation has to be weighed against roentgen irradiation. Even if the tumour can be radically removed there is a great risk of postoperative infection and haemorrhage. On the other hand, there seems to be no great experience with roentgen treatment. The

author tried roentgen treatment in the two inoperable cases in question with good result hitherto, and without complications. The treatment was given in accordance with the principles of FORSSELL's successful method for the treatment of cavernous haemangiomas. In such cases relatively small doses are given, only high enough to bring about progressive healing for a long time onwards similar to that occurring in the spontaneous healing of these tumours. The progressive diminution of the tumour is carefully observed and no renewed treatment is given as long as the tumour diminishes in size.

In the treatment of children with roentgen one must also bear in mind the risk of disturbances in the growth of the bones.

According to BLAND-SUTTON (quoted by FIGI) cystic lymphangiomas of the neck are seldom seen after puberty because previous infection causes either the patient's death or »spontaneous healing» (the infection destroys the endothelial lining, fluid is no longer formed and the cysts undergo regression (MOORE)). The author believes that, at least in most cases, the »spontaneous healing» is due to a natural involution of the tumour of the type that is often seen in cavernous haemangioma.

SUMMARY

Two cases of cystic lymphangioma of the neck with mediastinal involvement are described. Both were boys, 14 and 10 months of age on admission. The tumour was left-sided in both cases. In one case the neck part of the tumour was extirpated, but otherwise surgical treatment was impossible. Roentgen treatment was given, with rather small doses in accordance with the principles of FORSSELL's method for the treatment of cavernous haemangiomas. The patients have been followed for about 3 years and there have been considerable reductions of the tumours in both cases. There have been no complications, and the patients have no inconvenience from their tumour. The follow up is being continued.

ZUSAMMENFASSUNG

Es werden zwei Fälle von zystischem Lymphangiom des Halses mit mediastinaler Komponente beschrieben. Beide Fälle waren Knaben, bei der Aufnahme 14 bzw. 10 Monate alt. Der Tumor sass in beiden Fällen links. Im einen Falle wurde die zervikale Komponente entfernt, im übrigen aber waren die Tumoren inoperabel. Röntgenbehandlung wurde gegeben, und zwar ziemlich kleine Dosen, in Übereinstimmung mit der FORSELL'schen Methode zur Behandlung von kavernösen Hämangiomen. Die Patienten wurden etwa 3 Jahre lang verfolgt, und in beiden Fällen ist der Tumor bedeutend zurückgegangen. Komplikationen sind nicht aufgetreten, und die Patienten haben keine Beschwerden von dem Tumor. Sie werden weiter kontrolliert.

RÉSUMÉ

Description de deux cas de lymphangiome kystique du cou avec envahissement du médiastin. Les deux fois il s'agissait de garçons, agés de 14 et de 10 mois lors de leur

admission. Chez l'un et l'autre la tumeur était du côté gauche. Dans l'un des cas on extirpa la partie cervicale de la tumeur, mais à part cela le traitement chirurgical se montra impossible. On recourut à la radiothérapie, à doses plutôt faibles selon le principe de la méthode de FORSSELL pour le traitement des hémangiomes caverneux et des fibromes du cavum. Les malades ont été suivis pendant environ trois ans et chez tous deux une diminution considérable des tumeurs est survenue. Il n'y a pas eu de complications, et les patients ne sont pas gênés par leurs tumeurs. On continue à les surveiller.

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FROM THE RADIOLOGICAL DEPARTMENT OF CENTRALLASARETTET, UMEÅ, SWEDEN
(CHIEF: SVEN JUNGHAGEN)

CASES OF HAEMANGIOMA VERTEBRAE ROENTGEN TREATED WITH GOOD RESULTS[1]

by

Sven Junghagen

Until quite recently, Angioma Vertebrae has been considered as being a very rare disease. Now, however, with all the systematic examinations with the special technique used by SCHMORL, TÖPFE and JUNGHANNS, who found angioma in the spinal column in 10.93 %, 11.9 and 4.07 % respectively, we know that these are rather ordinary forms but that, for the most part, they do not occasion any clinical signs on account of their size and position. Similarly we know that the number of angiomata increases with age and that, in regard to sex classification, it appears that women are more predisposed than men (TÖPFER, 46 men, 54 women; HEANY and WITHAKER 2: 9). PERMAN thinks that the age of 20 is the most typical for angioma with clinical signs.

Angiomae are rounded or oval formations which can be localized anywhere in the spinal column without any special predilection as to place. In JUNGHANNS's opinion, however, the dorsal vertebrae appears to be the most exposed. Above all one finds them in the vertebral bodies as well as in the arches (PERMAN), in the spinous and transverse processes and in the articular processes as well. In size, angioma can vary from that of a pin's head to one covering the whole of the vertebral body. On the sectional surface it manifests itself as brown, somewhat sunken patches with often slightly spotty tinge in yellow. The surface is half glossy and of soft consistence. At times smaller crumbled particles of bone can be seen in the tumour. At the seat of the angioma the marrow is often absent entirely and the structure in the surroundings thinned and eroded.

Microscopically, angioma consists of large, rather irregular blood spaces which are covered with a thin layer of endothelium and a suggestion of adventitia, and are partly destroyed by larger or smaller amounts of fatty tissue which gives the surface a yellowish appearance. Limitation

[1] Submitted for publication May 29, 1947.

is poor and larger or smaller blood spaces continue into the marrow and communicate with the vessels. Within the tumour one finds necrotic or eroded laminae. Here and there one can even see signs of new formation in the form of single, coarse trabeculae covered with rows of osteoblasts which ROUX calls hypertrophying inactivity atrophy.

Roentgenologically one sees, at the seat of the angioma, a clarification of the structure with a disappearance of the thinner arcus spongiosa and with remaining individual coarse vertical trabeculae. Only one or other of these thin trabeculae, running horizontally, bind these together. If the angioma has occupied the whole vertebral body it becomes as if blown out by the disappearance of the normal concavity which is replaced by convexity. The vertebral body is compressed from increasing structural reduction, its width is increased and fractures can be established in the corticalis. In this way static deformities can also arise on the spinal column. Arches and apophysis can be more or less completely permeated with angioma which can lead to their being intensified. Isolated parts are considerably enlarged and turn into the spinal canal (PERMAN and GERHARD). When the corticalis has been penetrated, angiomatous tissue can grow out from the gaps to the surroundings for example posteriorly in the spinal canal where the tissues can either shoot in front of it periosteally or perforate it and spread itself peridurally (JUNGHANNS, GOLD amongst others). Laterally to the vertebral body it can give rise subpleurally to greater or smaller tumourous formations (MUTHMANN, GOLD amongst others).

As has been pointed out before, angioma seldom presents clinical signs on account of its size and position. On the other hand if it attains a considerable size or grows into the spinal canal it can develop medullary and neurologic signs (compression myelitis). This often takes place in the following manner:

(1) The angiomatous transformation of the vertebral body is followed by a blowing out of it with the bending of the present convex contour of the vertebra into the spinal canal producing pressure on the medulla or cauda These signs increase with the secondary compression of the vertebra (MUTHMANN) and an angular kyphotic formation (JUNGHANNS).

(2) Angiomatous tissue grows through the corticalis and causes subperiostal intensity (MAKRYCOSTAS, RIBBERT) or it grows in peridurally (GOLD, RIBBERT).

(3) Angiomatously transformed arches and apophysis press upon the medulla (PERMAN) or on outgoing root fibres.

Treatment in this disease must be symptomatic as radical removal of the tumour cannot come into the question and it is therefore a matter of first and foremost easing the pressure so that the neurological signs are removed. BEALY and BUCY consider »that the only treatment of avail

Fig. 1.

Fig. 2.

Fig. 3.

is laminectomy». KARSHNER and his colleagues warn against too severe surgical measures as the danger of haemorrhage is very great as is evident from the high mortality. THOMAS recommends operation (curettage) or radiological therapy and MEYERDING, like LIÈVRE, recommends roentgen treatment. RAMAGE mentions 5 operated cases of which 3 died immediately from haemorrhage and 2 recovered from roentgen: he also recommends a repetition of ray treatment if such is indicated.

Case 1. Persson, H. Born 1911. Labourer, Storliden, Sävar.

Admitted 28. 1. 1936 to Radiological Department, Umeå. Whilst working in the forest in April 1934, the patient slipped with his left foot and sustained a tear to the right of the small of his back and in the right gluteal region with immediate pains. After lying in bed at home for a week he was well. In January 1936 he felt pain in right gluteal region with »shooting pains» downwards and laterally along the right thigh when he walked. When lifting a pole on 21. 1. 1936 he got pains in the small of his back and down along the right thigh. No numbness or paresthesia.

From Status: Scoliosis thoracal. slightly convex to the left. Good mobility in the back which is without pain. Tenderness when bending extremely to the left. *Roentgen: Decalcification of vertebral bodies to L. 4, the thinned structures are traversed by denser trabeculae. The anterior parts of the vertebral corticalis appear defective and the other contours are deformed, pressed in. Similar changes observed in the arches. Tumour — angioma.* (Fig. 1.) *From 28. 1. to 17. 2., the patient received roentgen treatment (RT) posteriorly towards L. 4. 130 r. — 80 cm². 69 cm. — tin — 7 MA, in all 4,040 r. Improved.*

The patient returned on 14. 10. 1936. In June 1936 he felt pains from the right hip down along the back side of the leg to the foot and for the past two weeks similar pains in the left leg. Has a feeling of weakness. Numbness and paresthesia on front side of thighs. Has difficulty in walking on account of weakness in legs.

From Status: Power in dorsal flexors of foot and thigh greatly diminished. Sensitivity without comment. *Reflexes:* Patellar equally weak on both sides. Achilles somewhat weaker on the right leg. Babinski negative bilaterally. *Fresh RB towards L. 4 from right to left from 15. 10. to 27. 10. 1936. Total 2,000 r.×2. Pain reduced successively and status improved.*

From Status 16. 11. 36: Subjectively improved. At present has only feeling of stiffness in left hip and numbness along left thigh and left lower leg. No defecating or urinating trouble. No atrophy and no diminishment in gross power of lower extremities. Abdominal, patellar and achilles reflexes now stronger. Lasègue positive bilaterally at 70°. On 26. 1. 37 the patient complained of neuralgia of the ischiadic type when standing. Has tried to do lighter work but felt pains when lifting things. Lasègue negative S. R. 26 mm. *Rtg. photo (RF). Status unchanged.* On 30. 11. 37: all symptoms have now disappeared and gross power in both legs including hips, knees and ankles normal. Desires change in his mode of life and more work. After corresponding with the Institute for Cripples in Stockholm he was advised to undertake work of a not too strenuous nature to full capacity. *RF: vertebral bodies to L. 4 unchanged. The articular processes are now vacuolized.* (Fig. 2 and 3.) Sclerosis not visible. 13. 11. 39: was free from trouble until October 1939 when he lifted a heavy burden and ricked the small of his back which was accompanied during the course of the day by increasing pain in the leg and hip. After a week in bed, constant ischias. Says that the power in his right leg is less than in the left. Feels pain in the whole of the right leg and when he knocks his toes.

From Status: Back stiff and painful down to the lumbar region when bending forward. Has indirect tenderness. Lasègue positive, right leg, 70°, left leg negative. *RB from 17. 11 to 27. 11. 1939, 2,000 r × 2 (left and right).* 15. 10. 1940*:* Feels now considerably better and stronger. No pains. Walks steadily. *From Status:* neither direct nor indirect tenderness. No muscular atrophy. Gross power possibly somewhat less on left side? in hip, the same in knee and ankle. Patellar and achilles reflexes on right leg almost ceased but normal on left. RF: the transverse processes are now also attacked by almost complete absence of bony structure. *New RT 2,000 r. × 2.* On 1. 8. 1940: subjectively improved considerably, S. R. 9 mm. Can move around in the open without difficulty and pain. 13. 10. 1941: is now a carpenter. No trouble. The patient moves about smartly and easily. Lasègue negative. No reduction of gross powers, no direct or indirect tenderness. 1. 3. 45 (admitted to Medical Department for ulcus ventriculi). *Has been completely free from his trouble in the back and legs for two years. Has worked to full capacity. No atrophies or paresis. Sensitivity without comment. All reflexes lively. Lasègue negative bilaterally. S. R. 9 mm.* On 12. 5. 1947 his status was unchanged.

Case 2. Eriksson, K. G., 32 years, Solbacken, Skellefteå.

When carrying a heavy burden at the age of 16 he suddenly felt pains in his back and was »sick» for a month. Since then a gibbus has developed which has increased in size without pain or feelings of indisposition. Was treated at Nynäs in 1936 for insomnia. Has been unable to work since January 1937 on account of loss of power in his legs and a reduced ability to walk. Pain in knees. Insomnia. Admitted to Skellefteå Hospital on 15. 11. 38.

From Status: Gibbus 90 % thoracically, partly scoliotic and immobile. No direct or indirect tenderness. Gross power in lower extremities considerably diminished. Cannot lift legs from mattress. Knee-heel endeavour proceeds slowly and with difficulty wherein the heel glides outwards towards the tibia. Flexes kneejoint to 90°. Sensitivity: muscular impulses greatly diminished in toe joints. Sense of pain and touch in lower extremities. Intermittent jerks arise in the legs especially in the quadriceps. Staggers without any

Fig. 4.

ded tendency. Dragging walk with straight knees an turned-out feet. Sometimes stumbles as if his legs wi not carry him. LP: pressure 150. Queckenstedt's sig negative. WR negative. S. R. 35 mm. *RF* (JUNGHAEN): *Roentgen photos speak for angioma of thoracic ver brae medially in the kyphos with compression sign on the medulla.* (Fig. 4.) I suggest redressment treatment an then RB. After two weeks in gypsum bed the spa ticity in the lower extremities has diminished considerably. Foot and patellar clonus cannot be obtained fur ier forward. On 28. 3. 1939 the angle of the gibbus was 110°. Genua valga and pedes plani. Gross power in lower extremities greatly diminished. Cannot raise legs from mattress. Performs insignificant extension in knee joints if thighs are passively lifted; the same with the foot joints. Muscular impulse rather diminished. Similarly the sensitivity in the lower extremities is less than normal. Clonic jerks in leg muscles. No atrophy. *Reflexes:* Abdominal absent. Patellar clonus bilaterally. Foot clonus on right side. Babinski positive bilaterally. S. R. 10 mm. The patient was treated at home with gypsum cradle which he only used sporadically. *Admitted to Umeå Hospital Roentgen Department for RT on 10. 5. 1939 and from 10. 5 to 7. 6. 1939 was given 3,720 r in region of tumour (tin — 50 cm. — 7 MA). Returned on 21. 9. 39.* Gibbus increased.

From Status: motility in lower extremities = 0. Atrophy of muscles. An increase in the reduction of sensitivity which increases down towards the feet. Patellar and foot clonus. Abdominal reflex weakly positive. Cremaster reflex bilaterally negative. Babinski bilaterally positive. S. R. 3 mm. *RT from 2. 10. to 6. 10. 2,360 r.* On 6. 10. 39 consulted surgeon for eventual laminectomy, »suggest waiting for time being for result of RB as the vertebral bodies are too brittle for the present to resist such an action» (OLIVECRONA). Patient discharged and readmitted 14. 7. 1941. Has looked after himself admirably and lain in gypsum cradle. Marked improvement in spring 1941 in that the pains in the knees and the clonic spasms in the legs have ceased. Mobility in the lower extremities returned peripherally, advancing upwards. Began trying to walk in April and can now move around and go up and down stairs with the aid of a stick. No miction or defecation trouble.

From Status: No change in deformity in back. Strong valgus position in knees and pes planus cum hallux valgus. Walks stumpily without support. No muscular atrophy. Spinal nerves: lower legs and feet in hanging position blue coloured and swollen. No certain diminishing of gross power in joints of hips, knees or feet. Can genuflect but not squat and can stand on toes and heels. Superficial and deep sensitivity without comment. Walks rather uncertainly. Possibly somewhat paretic (valgoid knees). Reflexes: Patellar and medial plantar positive. No clonus phenomena. Babinski bilaterally positive. *Has now received a fresh RT on the 15. 7. to 22. 7. 41 of 1,000 r from right to left towards the region of the tumour.* Sent home and returned in February 1942. Condition greatly improved. Walks about the house without a stick. No spasms, cramps or pain. Gets tired in his back quickly. The neurological examination presents an entirely unchanged picture. *Fresh RT of 1,180 r from right to left.* Home. *Examined by Dr.* FRANKE *at Skellefteå on 21. 6. 45: Babinski reflex bilaterally positive. Strong diminishing but not cessation of muscular impulse in toes accompanied by a disturbance in his walk which later has no typically neurologic character but which is certainly caused by a double-sided deformity of the foot. Sensitivity for touch and pain without comment.* Lively quadricpes reflexes bilaterally. No foot clonus. Calf reflexes bilaterally weak (obtained only in the Babinski position). Of the abdominal

reflexes the lower one is absent. No ataxy. Normal muscular tone. *RF unchanged. Re-examined on 21. 4. 1947* (FRANKE). Now complains of a persistent, gnawing pain in both legs which he has felt ever since August 1946.

From Status: Psyche clear and alert, schizoid. Cranial nerves without comment. Motility: No stiffness in neck. Lasègue negative. Gross power of both legs moderately diminished but no paresis. Can stand on toes and heels even on one leg at a time. Moderate atrophy of thigh muscles. Circumference 20 cm above patella: right leg 50.5, left leg 51.5. Circumference of calves, right and left 36 cm. Intermittent contractions similar to clonus occur in left calf muscles. Otherwise no hypercinesia. Sensitivity without comment. Muscular impulse diminished but not absent for movement of toes. Reflexes: Pupils round, react remarkably slowly and insignificantly for light and near sight. Abdominal reflexes lively. Patellar and achilles ++ and + respectively. Babinski right negative, left positive, Rossilimo bilaterally negative. RF: considerable kyphoscoliosis with pronounced gibbus between 7th and 9th thoracic vertebrae. The structure in T. 8 and T. 9 is coarse meshed and the anterior parts of these vertebral bodies are grown together into practically one completely destroyed intervertebral lamina. The net-formed coarse meshedness of these vertebral bodies present a typical appearance of vertebral haemangioma. A moderate number of deforming deposits can be seen on the edges of the neighbouring vertebral bodies. Otherwise there are no tumour-suspect destructions to be found. In comparison with the pictures from 1938, the deformities in the back are unchanged whilst the structure of the vertebral bodies in the changed parts appear to have become more coarse meshed now (HEINZE).

The cases related above are young men who got their first signs in almost identical manners in that the first, at the age of 25, sustained a tear in the small of his back whilst working whereas »case 2» was stricken at the age of 16 when carrying a heavy burden and when a gibbus appeared simultaneously in the thoracic vertebrae which later grew in size. At a subsequent roentgen examination it appeared that this sign was caused by a tumourous destruction of haemangioma localized to L. 5 and T. 8 and T. 9 respectively (Case 2). In case 1, it was not only the vertebral body but also the arches and processes that were attacked and it seems that the destruction within these latter parts has proceeded whilst the changes in the vertebral bodies remained stationary. In case 2 no change within the affected region could be established and whilst the roentgen picture in case 1 is typical for this disease, it seems to me that the appearance of the vertebral bodies, with their tendency to being wedge-formed and the hyperostotic formation of the ridge round the destroyed cartilage lamina, departs from the usual picture; to a large extent this contributes to the very powerful kyphoscoliosis which showed tendencies to increase during the first years of treatment. The typically changed structure, however, leaves no doubt as to its nature.

The different localization of the tumours in both of these cases entails that the signs manifested in connection with it appear to be so different. The position of L. 5 below the medulla spinalis therefore entails the absence of medullary signs and so Case 1 presents chiefly the picture of a radiculitis with pains, paresthesia and a tendency to slight paresis which

sign always yields to the roentgen treatment given in order, finally, to cease altogether. The localization of the processes of T. 8 and T. 9 (in Case 2) and the simultaneous presence of the static deformity leads to the typical compression myelitis, typical of these localizations, and which here cause a complete paraplegia with a positive Babinski which still remains on the left side whilst the other signs of the compression myelitis must, to a large extent, be considered as having ceased.

In both cases the treatment has been mainly Roentgen. In case 2, a redressment treatment with a gypsum cradle has also been resorted to. From January 1936 to October 1940, case 1 received 16,040 r in the direction of the tumourous region and case 2, from May 1939 to February 1942, received 9,260 r. The rays were hard filtered (tin) and were administered at a distance of 60 cm and 50 cm respectively with 7 MA and 190 KV. The treatment was administered twice a day (morning and evening) in the hope that the short intervals might further increase the effect. As I previously pointed out, an improvement could be established after each treatment series in case 1 even though a relapse could be noticed until August 1940 from which time the improvement steadily advanced and he has been fully employed as a carpenter since 1941. Case 2 is worthy of note in that after the beginning of the treatment in May 1939, an improvement was first noticed in the spring of 1941. The paraplegia and pains then began to recede and the sign has to a great extent now disappeared. The last neurological examination on 21. 4. 47, showed only a moderate diminishing of the gross power of the legs and no paresis. The patient was able to stand on toe and heel on one leg at a time! Moderate atrophy of the thigh muscles. Muscular impulse reduced but not absent for movement of the toes. Babinski negative right and positive left!

The above results seem to me to be a remarkable proof of the suitability and success of roentgen therapy in haemangioma vertebrae if only it is carried out energetically with due observation of the necessary precautions. Good results have been mentioned by ROITH and Mme LABORDE who, like LIÈVRE, emphasize the good effects of roentgen especially for the pains occurring in this disease. My cases seem to me as being also proof of valuable results in that the treatment in Case 1 finished in 1941 and that this man is free from signs despite heavy work. The treatment in case 2 terminated in 1942 and, as appears from his medical history sheet, he is as good as restored both subjectively and objectively.

SUMMARY

The author describes two cases of haemangioma vertebrae with grave neurological changes, which could be reduced by means of roentgen therapy.

ZUSAMMENFASSUNG

Der Verf. beschreibt zwei Fälle von Haemangioma Vertebrae mit schweren neurologischen Veränderungen, welche Symptome nach Röntgenbehandlung zum Zurückgehen gebracht werden könnten.

RÉSUMÉ

L'auteur décrit deux cas d'hémangiomes vertebraux accompagnés de graves lésions neurologiques qu'on a pu faire rétrocéder par la radiothérapie.

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SERVICE DE CURIETHÉRAPIE (CHEF: SIMONE LABORDE) À L'INSTITUT DU CANCER, PARIS

LE TRAITEMENT DES ANGIOMES TUBEREUX DES JEUNES ENFANTS[1]

par

Simone Laborde

L'emploi du radium ou des rayons roentgen dans le traitement des angiomes tubéreux des jeunes enfants est redouté par un certain nombre de médecins, parfois à juste titre, semble-t-il: c'est qu'ils connaissent les accidents qui peuvent survenir chez les tout-petits sous l'action des rayonnements.

Cependant, il ne faut pas imputer à une méthode les erreurs de ceux qui l'appliquent selon une technique défectueuse, erreurs qui consistent à utiliser des doses trop importantes de rayonnements sans souci de l'extrême radiosensibilité des tissus des jeunes enfants.

Avant de décrire les modes de traitement qui me sont habituels je rappellerai les accidents que j'ai pu observer. Ils résultent toujours d'un excès de dose et d'une mauvaise technique.

Accidents. — Ils sont de divers ordres et intéressent les parties molles, le système osseux et le système nerveux central.

Au niveau des parties molles ce sont des *radiodermites chroniques* atrophiques et scléreuses, parfois avec perte de substance, intéressant la peau et les tissus mous sous-jacents, et apparaissant à plus ou moins longue échéance après le traitement. L'interrogatoire révèle toujours dans ces cas la présence d'une radiodermite aiguë, d'importance variable au moment de l'application de rayons roentgen ou de rayons du radium. Il est à noter que les cicatrices dischromiques ne s'améliorent pas quand l'enfant grandit, bien au contraire. Elles s'étalent et s'étendent, elles sont comme étirées, dépassant les limites de l'angiome traité, surtout dans les régions où les téguments sont lâches comme le dos, l'abdomen, le creux sus-claviculaire par exemple.

Au niveau du *système osseux*, les lésions siègent au niveau des os longs ou des os plats. Quand elles intéressent les os longs, ce sont des ar-

[1] Remis à la Réd. le 31 Mai 1947.

rêts de croissance après irradiations pratiqués au voisinage des épiphyses, phénomènes bien en accord avec l'expérimentation poursuivie chez les jeunes animaux. Ces irridations consistent généralement en applications d'appareils moulés en cire supportant des tubes de 10 mg Ra (filtration 1.5 mm Pt) et laissés en place 48 heures ou même davantage. Quand l'appareil supporte 60 à 80 mg Ra, on conçoit que la dose de rayonnement qui traverse de part en part la pièce osseuse puisse arrêter la croissance. D'autres cas ont été observés après applications de rayons roentgen à doses massives.

Au niveau des os plats, crâne ou face, les lésions se traduisent dans les cas légers par une dépression osseuse plus ou moins marquée, qui n'est pas visible, mais la palpation permet de sentir l'enfoncement de la table externe qu'entoure un léger rebord osseux. On a pu constater également les dissymétries faciales tout comme dans les vielles expériences de TRIBONDEAU et RÉCAMIER (1905) irradiant au moyen des rayons roentgen la tête des jeunes animaux. Dans les cas graves, heureusement tout à fait exceptionnels, il peut s'agir d'une véritable ostéo-radionécrose.

Les radio-lésions peuvent atteindre aussi le *système nerveux central*, après applications effectuées sur le crâne des jeunes enfants. J'en ai connu un cas chez un bébé traité pour un angiome du front par une application de radium filtré, prolongé 24 heures. L'enfant a présenté dans la suite des parésies de divers groupes musculaires, une gêne de la parole avec phénomènes de dysarthrie impossibles à rattacher à aucun syndrome connu. Sont-ils dus à une action directe sur les éléments nerveux jeunes? Il est difficile de le savoir. Il est cependant plus probable qu'il résultent de la rupture des capillaires et de petites hémorragies internes.

Traitement. — Laissant de côté les angiomes des adultes et les angiomes plan (taches de vin), je ne m'occuperai que des angiomes des enfants (hémangiomes tubéreux, caverneux) qui affectent la forme de tumeurs sous-cutanées parfois volumineuses avec coloration plus ou moins rouge de la peau. On sait qu'ils s'accroissent parfois rapidement au cours des premiers mois de la vie.

D'une manière générale, j'utilise plus volontiers le radium que les rayons roentgen car il est d'un maniement plus commode chez les jeunes enfants. Toutefois, il est possible que la *contact-thérapie* que nous étudions actuellement puisse rendre les mêmes services quand la technique en sera bien réglée.

Avec le radium, d'excellents résultats peuvent être obtenus pour les doses extrêmement faibles, car il ne s'agit pas d'obtenir une destruction cellulaire, mais une sclérose des vaisseaux néoformés. Or, celle-ci s'effectue très lentement et d'une manière progressive sous l'action de doses de rayonnement parfois tout à fait minimes. C'est un traitement qui demande de longs mois sinon des années et doit être poursuivi avec une lon ue

Fig. I. Enfant B. O. R., 8 mois.
Angiome du cuir chevelu, rouge vif, saillant. Traité par appareil émaillé 2 × 2 cm contenant 16 mg Ra (filtre = liège: 2 mm). Deux applications, l'une de 8 minutes, l'autre de 10 minutes à 6 mois d'intervalle.

Fig. I Bis. Enfant B. O. R., 1 an.
Après traitement. L'angiome a complètement disparu, sans alopécie.

patience, si l'on veut obtenir un résultat esthétique parfait se mettre à l'abri d'accidents. J'ai été ainsi amenée au cours des années à n'utiliser que des doses de plus en plus faibles et à diminuer et espacer le nombre des applications jusqu'à n'en effectuer parfois que deux ou trois.

Appareils. — Les appareils utilisés sont de deux genres: des *émaux radioactifs* et des *aiguilles*.

Les émaux sont constitués par un support métallique, le plus souvent en cuivre, auquel adhère intimement un émail où se trouve incorporé le radium (Brays plaque). Ils sont de dimensions variées, leur teneur en radium peut aller de 0.5 mg à 4 mg par centimètre carré.

Leur filtration comporte seulement 2 à 3 mm de liège, c'est à dire que le rayonnement α est complètement éliminé, mais que la presque totalité du rayonnement β et tout le rayonnement γ sont utilisés.[1]

Il faut bien savoir que, contrairement à une opinion souvent exprimée, le rayonnement β n'exerce une action caustique qu'au delà d'une certaine dose. Il en est de même d'ailleurs du rayonnement γ qui n'offre à ce point de vue qu'une fausse sécurité car, malgré la faible énergie qu'il abandonne aux tissus, on sait qu'il peut entraîner des radiodermites graves et des lésions tissulaires profonds.

[1] On peut également employer de petits boitiers en acier Monel de 3/10 de mm d'épaisseur laissant passer le rayonnement β dur.

Fig. II. Enfant D. U. H., 12 mois.
Angiome du bout du nez. Traité par appareil émaillé 2 × 2 cm contenant 16 mg Ra (filtre = liège: 2 mm). Quatre applications de 10 minutes chacune, alternativement sur chacun des deux côtés du nez, à 3 mois d'intervalle.

Fig. II Bis. Enfant D. U. H., 11 ans.
Après traitement. Disparition de l'angiome sans aucune cicatrice.

Les appareils à rayonnement β ne comportent que des applications de courte durée, et permettent d'obtenir le résultat cherché sans aucune réaction cutanée. Par ailleurs, ils laissent passer la totalité du rayonnement γ qui agit en profondeur pour provoquer une sclérose vasculaire mais sans aucun risque d'altérer les organes profonds, étant donné la faible dose qui y parvient. La décoloration s'effectue lentement en même temps que la diminution de volume.

Lorsqu'aucune réaction cutanée n'est survenue au moment même du traitement, il n'y a pas lieu de craindre pour l'avenir l'apparition de télangiectasies, de pigmentation ou d'atrophie cutanée, altérations qui ne surviennent que si l'on a multiplé les irradiations ou prolongé les temps d'application d'une manière intempestive.

J'utilise également, et surtout pour le traitement des angiomes volumineux, des aiguilles contenant 1 ou 2 mg de radium-élément dont la longeur varie de 1.5 cm à 2.5 cm. Leur filtration est de 0.5 mm de platine.

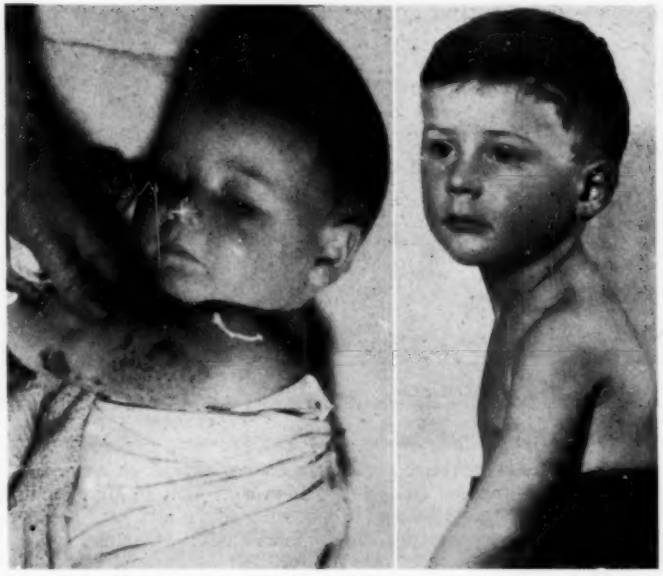

Fig. III. Enfant C. A. M., 6 mois.

Gros angiome cutané et sous-cutané de la face postéro-externe du bras gauche. Traité par appareil émaille 5 × 3 cm contenant 8 mg Ra (filtre: 2 mm liège). Trois séries d'application de 15 minutes chacune sur 3 régions différentes, au cours d'une année.

Fig. III Bis. Enfant C. A. M., 2 ans.

Après traitement. Disparition totale de l'angiome.

Ces aiguilles sont le plus souvent utilisées en *curiepuncture*, surtout depuis une dizaine d'années. Mais dans les années précédentes j'ai parfois employé des dispositifs externes constitués par une lame malléable d'aluminium de 2/10ème de mm d'épaisseur sur laquelle on dispose, en les maintenant avec un sparadrap adhésif, des aiguilles ou des tubes de faible teneur (ex. fig. VII et IX).

La durée des applications des émaux radioactifs dépend bien entendu de leur teneur en radium, de leurs dimensions et de l'âge de l'enfant, elle peut varier de 10 à 40 minutes.

Les légendes des figures ci-jointes serviront d'exemples et d'indications.

Age. — L'âge auquel il convient de traiter un angiome reste une question très discutée, car il est certain que plus l'enfant est jeune, plus l'angiome est sensible, mais plus aussi le sont les tissus généraux. Il

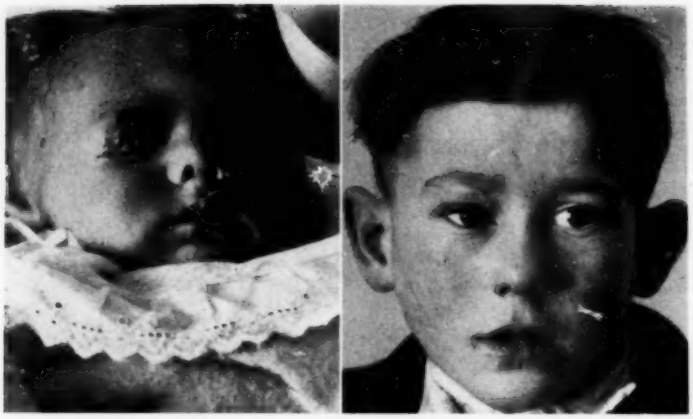

Fig. IV. Enfant G. A. S. P., 3 mois.

Angiome de la paupière supérieure droite, cutané et sous cutané, ulcéré. Traité par appareil émaillé 2 × 2 cm contenant 16 Mg Ra (filtre = liège: 2 mm). 1ère application d'une durée de 6 minutes, paupière relevée. Deux autres applications de 10 minutes chacune, au cours de l'année.

Fig. IV Bis. Enfant G. A. S. P., 9 ans.

Après traitement. Disparition totale de l'angiome. La paupière reste légèrement épaissie.

faut donc tenir compte de ces deux facteurs contradictoires dans la conduite du traitement. On peut, d'après notre expérience, traiter un jeune bébé de 2 ou 3 mois sans danger, à la condition que cette première application soit très faible (fig. IV).

Cette première application suffit presque toujours à arrêter l'extension de la tumeur. On a alors le loisir d'attendre que l'enfant atteigne 5 ou 6 mois, âge auquel les risques sont bien moins grands. On pourra ensuite faire une deuxième, puis, une troisième application à 3 ou 4 mois d'intervalle ou davantage. Après 3 ou 4 applications, il faut attendre au moins 10 à 12 mois avant de poursuivre le traitement, ce qui est rarement nécessaire. Il arrive que des angiomes qui n'ont pas complètement disparu après deux années ne laissent plus de traces lorsqu'on revoit les jeunes sujets après cinq à six ans.

Il faut noter que les applications de radium effectuées sur les angiomes ulcérés qui saignent arrêtent rapidement les hémorragies dès la première ou la seconde application.

Les angiomes volumineux sont traités par curiepuncture; les aiguilles étant complètement enfouies, au sein même; du tissu angiomateux, à raison d'une aiguille contenant 2 mg Ra pour un volume de tissue de

Fig. V. Enfant P. I., 6 mois.

Gros angiome cutané et sous-cutané de la région sus-claviculaire gauche ulcéré ayant donné lieu à des hémorragies profuses. Traité par appareil emaillé 5 × 3 cm contenant 8 Mg Ra (filtre = liège: 3 mm). Série de 3 applications, successivement sur 2 régions: la première d'une durée de 10 minutes; la seconde de 25 minutes; la troisième de 30 minutes, au cours d'une année.

Fig. V Bis. Enfant P. I., 4 ans.

Après traitement. Affaissement complet de l'angiome. La peau est souple, mais persistance d'une cicatrice dischromique, due à l'ulcération spontanée du début.

3 à 4 cm³ environ. L'aiguille doit être suffisamment éloignée du plan osseux et entourée de tissus mous. La durée d'application est de 2 à 8 heures, suivant l'âge de l'enfant. La tumeur s'affaisse lentement et se décolore, sans réaction d'aucun genre et le point d'implantation des aiguilles demeure absolument invisible.

Pour de très gros angiomes, il est prudent de ne pas traiter la totalité de la tumeur en un seul temps, mais de la diviser en plusieurs aires qui seront irradiées successivement.

Etant donné le petit volume des membres ou la faible épaisseur du massif facial des bébés on doit tenir compte avec soin de la *dose totale*, l'étendue de la surface irradiée jouant un rôle primordial. C'est en s'appuyant uniquement sur les doses données par centimètre carré ou centimètre cube, qu'il s'agisse d'aiguillage, d'appareil moulé à faible distance ou d'émaux radioactifs, que l'on est amené à de fatales erreurs.

Les doses que nous indiquons sont fort éloignées de celles qu'on

Fig. VI. Enfant G. U. C., 2 mois.

Gros angiome cutané et sous-cutané de la région nasale et de l'angle interne de l'œil. Traité par appareils émaillés: Une première application d'une durée de 15 minutes avec appareil émaillé de 2 × 2 cm contenant 16 Mg Ra (filtre = liège 3 mm). Dans les cours de l'année deux autres applications d'une durée de 30 minutes avec appareil émaillé 5 × 3 cm contenant 8 Mg Ra (filtre = liège: 3 mm). La disparition s'effectue lentement.

Fig. VI Bis. Enfant G. U. C., 18 ans.

Guérison parfaite, aucune cicatrice visible.

trouve consignées dans maintes observations de traitement, elles sont dans bien des cas 10 à 100 fois moins élevées si on les compare, par exemple, à celles qui résultent de l'emploi d'appareils moulés en cire de 1 cm ou 1.5 cm d'épaisseur, supportant 30, 50 mg de radium élément ou davantage en tubes filtrés (0.5 ou 1 mm de platine), laissés en place plusieurs heures ou même plusieurs jours, ou encore d'applications d'un grand nombre d'aiguilles et parfois pour des durées excessives.

Ce sont ces applications prolongées qui, en permettant au rayonnement γ d'agir dans la profondeur à dose élevée, provoquent les accidents auxquels j'ai fait allusion. Il faut de même condamner les applications prolongées ou trop fréquemment renouvelées d'appareils à rayonnement β.

L'ensemble de ces considérations s'applique aussi au traitement par les rayons roentgen. Certes, c'est une méthode tentante, surtout pour le traitement des angiomes volumineux, mais l'emploi de larges portes d'entrée, surtout au voisinage des épiphyses, augmente beaucoup les risques en raison des doses importantes qui parviennent dans la pro on-

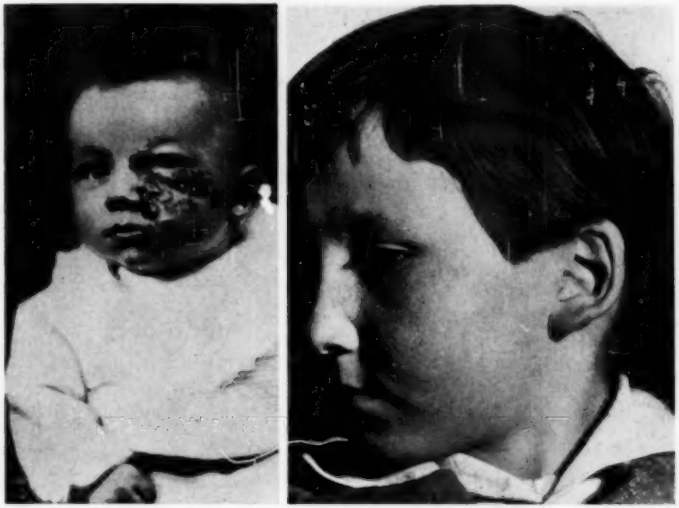

Fig. VII. Enfant B. E. R. N., 5 mois.

Très gros angiome cutané et sous-cutané de la face. Traité par un appareil de surface composé d'une lame d'aluminium de 0.2 mm d'épaisseur sur laquelle sont disposées en quinconce 10 aiguilles de 2 mg Ra (filtration: 0.5 mm platine). Trois applications d'une heure chacune sont effectuées au cours d'une année. 18 mois après, affaissement complet avec persistance de quelques télangiectasies.

Fig. VII Bis. Enfant B. E. R. N., 9 ans.

Après traitement. Disparition totale de l'angiome et des télangiectasies précédemment notées. La peau est tout à fait normale.

deur des tissus. Sans doute les doses de rayons roentgen pourraient-elles être très inférieures à celles qui sont habituellement employées.

La révision des petits malades traités à l'Institut du Cancer de 1924 à 1943, et qui comprend 315 observations, confirme les remarques qui précèdent. Il en est de même d'une centaine d'enfants vus en clientèle privée.

Ces enfants ont été examines de *deux à dix-huit ans après* leur traitement. Le recul est donc largement suffisant pour que l'on puisse juger de la valeur esthétique des résultats éloignés.

Dans cet ensemble, nous n'avons jamais observé d'accidents de notre fait, ni radiodermite, ni atrophie osseuse, ni musculaire. Jamais le traitement des angiomes du cuir chevelu n'a entrainé d'alopécie, celui des angiomes des paupières n'a pas empêché la pousse des cils ni créé le moindre trouble oculaire.

Fig. VIII. Enfant V. I. E., 6 mois.

Angiome monstrueux de la moitié gauche de la face en voie d'accroissement rapide avec participation de la muqueuse de la joue et du voile du palais. Traité par curiepuncture au moyen d'aiguilles de 2 mg Ra (filtration 0.5 mm platine). Une première application comporte l'emploi de 4 aiguilles pour une durée de 2 heures. Deux autres curiepunctures de 2 heures chacune avec 2 aiguilles, en des zônes différentes, au cours d'une année amènent une diminution considérable, non seulement de l'angiome cutané mais de la partie muqueuse intra-buccale de la tumeur. Deux ans après, application de l'appareil émaillé 2 × 2 cm contenant 16 mg Ra (filtre = liège: 2 mm) durée 10 minutes au niveau de la lèvre supérieure.

Fig. VIII Bis. Enfant V.I.E., 5 ans.

Après traitement. Disparition totale de l'angiome. Persistance d'une peau légèrement frippée au niveau de la lèvre supérieure.

Sauf pour les angiomes ulcérés, qui laissent toujours une cicatrice marquée, quel soit le mode de traitement utilisé, les résultats esthétiques sont la règle. Nous avons cependant noté quelques cicatrices dischromiques légères, elles répondent à des traitements effectués entre les années 1924 et 1929 avec des applications de radium trop prolongées ou trop fréquentes, suivant un mode de traitement que nous avons abandonné.

Les angiomes tubéreux irradiés dans les conditions techniques que je viens de rappeler ont donc disparu sans laisser de traces ou avec des traces minimes. Parfois certains angiomes épais montrent, après disparition, une peau souple, normalement colorée, mais celle-ci reste le ère-

Fig. IX. Enfant M. A. T., 6 mois.

Gros angiome monstrueux de la face. Traité par appareil de surface composé d'une lame d'aluminium de 0.2 mm d'épaisseur sur laquelle sont disposés 6 tubes de 5 mg Ra (filtre 0.5 mm platine) disposée en quinconce: Quatre applications à 3 mois d'intervalle de 1 heure $^1/_2$, puis de deux heures de durée. L'enfant est perdu de vue jusqu'en 1936: diminution considérable. Nouveau traitement par curiepuncture: 3 aiguilles de 2 mg Ra (filtre: 0.5 mm platine). Durée 3 heures.

Fig. IX Bis. Enfant M. A. T., 4 ans.

Après traitement. L'enfant a de nouveau été perdu de vue et le traitement inachevé. L'angiome est affaissé, l'œil complètement dégagé mais il persiste une cicatrice qui sera traitée ultérieurement.

ment plissée, comme si elle n'avait pu se rétracter en même temps que la tumeur sous-cutanée. L'aspect est alors analogue à celui des angiomes qui ont disparu spontanément.

Ce sont là des résultats qu'à notre avis aucune autre méthode de traitement ne peut permettre d'obtenir.

Certes, aucun de nous n'est à l'abri d'une faute de technique, d'une erreur de dosage, mais je pense que l'on doit condamner les techniques d'emploi du rayonnement du radium à doses élevées en applications prolongées ou trop répétées, et des doses importantes de rayons roentgen à grande puissance chez les jeunes enfants dont les tissus sont d'une extrême sensibilité.

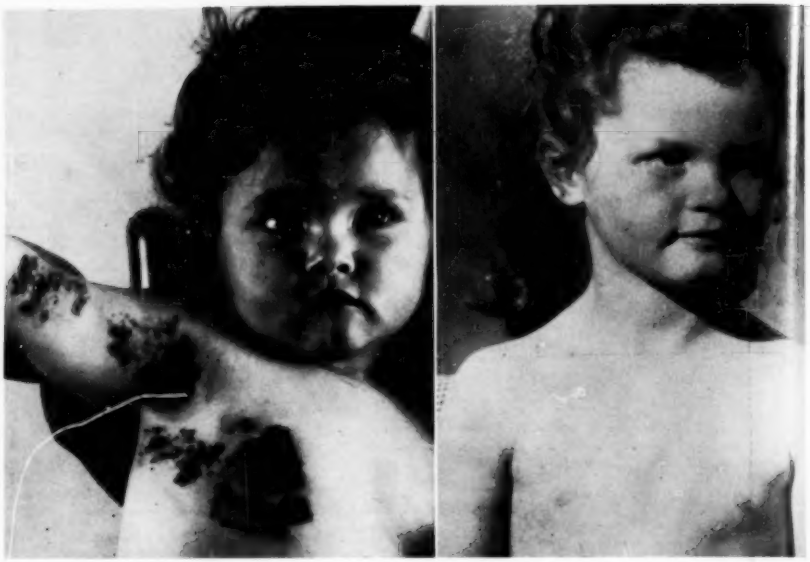

Fig. X. Enfant F. E. R., 7 mois.

Angiomes multiples très colorés, peu surélévés, aspect grenu. Traité au moyen d'un appareil émaillé 5 × 3 cm contenant 8 mg Ra (filtre: 2 mm liège) par trois séries d'application d'une durée de 20 minutes sur chacune des régions atteintes. En tout, trois applications par région en l'espace de 10 mois.

Fig. X Bis. Enfant F. E. R., 4 ans.

Après traitement. Disparition totale, sans aucune trace visible.

RÉSUMÉ

Les rayons roentgen et les rayons du radium, quand ils sont employés à doses trop élevées dans le traitement des angiomes tubéreux des jeunes enfants sont responsables d'accidents de divers ordres: lésions cutanées, arrêts de croissance des membres, accidents nerveux. L'auteur préconise l'emploi de *doses minimes* soit au moyen d'appareils plats émaillés permettant d'utiliser le rayonnement β, soit au moyen d'aiguilles contenant 1 ou 2 mg Ra (filtration: 0.5 mm Pt) utilisées pour la curiepuncture des angiomes volumineux. Une série de photographies démontre les bons résultats esthétiques de cette méthode.

SUMMARY

When employed in too high doses in the treatment of tuberous angiomas in small children roentgen and radium rays are responsible for various accidents: cutaneous lesions, ceased growth of limbs, nervous accidents. The author proposes *minimum doses* either by means of flat enamelled containers allowing the use of β-rays, or by means of

needles containing 1 or 2 mg Ra (filtration: 0.5 mm Pt) for the curiepuncture of voluminous angiomas. A series of photographs demonstrates the satisfactory æsthetic results of this method.

ZUSAMMENFASSUNG

Wenn Röntgen- oder Radiumstrahlen für die Behandlung von tuberösen Angiomen bei Kindern in zu grossen Dosen angewandt werden, verursachen sie Schäden verschiedener Art: Hautschädigungen, Wachstumshemmungen, nervöse Störungen. Verf. schlägt *Minimidosen* vor, entweder mittels emaillierter Planpräparate, welche die Anwendung von β-Strahlen gestatten, oder durch Curiepunktion mit Nadeln, 1 oder 2 mg Ra enthaltend (Filtrierung: 0.5 mm Pt). Eine Reihe Photographien zeigt das gute ästhetische Resultat dieser Methode.

FROM THE DEPARTMENT OF GYNECOLOGY (HEAD: PROFESSOR J. HEYMAN),
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CLINICAL AND EXPERIMENTAL OBSERVATIONS IN RADIOTHERAPY IN FUNCTIONAL UTERINE HAEMORRHAGE

(A preliminary Report)[1]

by

Hans Ludvig Kottmeier, M. D.

The etiology and pathogenesis of abnormal uterine haemorrhage in women of the reproductive age, which is not due to an apparent lesion of the genital organs, vary widely in different patients. Particularly in American literature this type of haemorrhage has been termed functional haemorrhage. This term indicates that a disturbance of the ovarian function is the underlying cause of the changes found in the endometrium and myometrium of patients manifesting menorrhagia or metrorrhagia. Opinions differ as regards the significance of the term abnormal functional haemorrhage. Some authors consider abnormal uterine bleeding as functional if its cause cannot be demonstrated in the genital organs. Others again, use this term in the absence of any apparent organic process responsible for the haemorrhage. According to the latter concept the type of haemorrhage, which coexists with cardiac diseases, sequels of infectious processes in the abdominal or pelvic organs, pathologies of the thyroid gland, and so forth, would thus not be functional. Apart from this difference of opinion as regards the classification of abnormal haemorrhage, it is frequently difficult to determine whether this disorder is due to an organic lesion of the genital organs or not. This does not only apply to cases of myoma of the uterus. In a recent comprehensive paper I called attention to the fact that differential diagnosis between uterine polypi and irregular endometrial hyperplasia has hitherto not been given sufficient consideration when assessing curettage material. I also stated that there are many indications that uterine polypi are probably much more common than can be surmised from a study of the literature It

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seems reasonable to apply the term functional bleeding to abnormal uterine haemorrhage in the absence of any lesion of the genital organs, which might be responsible for this disorder. In order definitely to be able to rule out this possibility, it is of fundamental importance not only to obtain an accurate past history, particularly information as to the type of bleeding present, but also to subject the patient to a careful medical and gynaecological survey including intrauterine exploration and diagnostic curettage. The histological examination of the endometrium frequently is a valuable guide in determining whether haemorrhage is ovulatory or anovulatory. This differential diagnosis is of major importance not only in assessing the pathogenesis of this disorder but also in planning the therapeutic programme. The endometria of patients suffering from the same type of haemorrhage may show different histological characteristics. Particularly in metrorrhagia the appearance of the uterine mucosa usually conforms to that of a proliferative endometrium showing either more or less marked pathological hyperproliferation or cystic glandular hyperplasia. Abundance of glands, glandular dysplasia, density of the stroma and its content of precollagen and collagen fibrils, the degree of the swelling of the stroma cells, and so forth, vary widely in different cases. At Radiumhemmet in Stockholm, curettage was performed one time or on several occasions on 772 patients suffering from recurrent climacteric haemorrhage. It was found that the biopsies obtained from one and the same patient on different occasions often showed the same histological characteristics. In this connection it should be borne in mind that the degree of the shedding of the uterine mucosa may affect the general appearance of the endometrium. As regards the histological control of the curettings it is — according to our experience — fundamentally important to study carefully the histological structures giving particular attention to the appearance of the epithelial cells, the content of collagen fibrils of the stroma, and the degree of activity of the stromal cells. If these factors will be given more serious consideration in the future, it will perhaps be possible to classify the pathological proliferative uterine mucosas. It is not unreasonable to assume that in metropathia haemorrhagica cystica the proliferative uterine mucosa might be correlated to the considerable variations in urinary excretion of oestrogenic hormone, which were observed by some medical authors as well as by us. This classification would probably be important also in planning therapeutic measures. A point worthy of mention is that some gynaecologists report to have obtained favourable results with oestrogenic hormone, whereas others are definitely against this therapy.

In evaluating a pathological proliferative endometrium it should be borne in mind that the physiological proliferative uterine mucosa, and

marked cystic glandular hyperplasia are poles in a progressive development. Clinical observations and mainly experimental studies in both human beings and animals support this view. Although from a practical and clinical point of view it may be reasonable to speak of different stages in the development of a pathological proliferative uterine mucosa, it should be borne in mind that the transitions between these stages are not well defined, and therefore the different stages should not be considered as separate entities. FALCONER, and several other authors, do not seem to have given sufficient consideration to this fact, and their argumentation is therefore inconclusive. The difficulty in determining whether FALCONER's attempt at classifying the pathological proliferative endometrium is justified, is further increased by the following facts: In the first place FALCONER's terminology is not fully satisfactory, and secondly, it seems to have escaped the attention of this author that the morphological changes identified in curettings are dependent, to some extent, on the time, when the biopsies were taken in the phase of desquamation. FALCONER does not always differentiate between the terms metropathia haemorrhagica cystica and cystic glandular hyperplasia though the former is a pathophysiological concept rather, whereas the latter is a morphological concept.

It is well known that pathological changes in the ovaries are frequently demonstrable in cases of functional bleeding (SCHRÖDER, KJÆRGAARD, R. MEYER, E. NOVAK, TIETZE and others). It is not evident, however, that the primary cause of menstrual disorders should invariably be looked for in the ovaries. Apart from having to take a uterine factor into account — an eventual disturbance of the blood circulation in the uterine mucosa, for instance, — menstrual disorders often point either to an endocrine dysfunction (GRUMBRECHT, HAMBLEN, FREDRIKSON and others), or to dysfunction of the autonomic nervous system. It has long been known that a psycho-neurotic strain may cause a disturbance of the ovarian cycle. The investigations of STIEVE, LUFT, MAYER, and others, have brought forward scientific evidence in support of this fact. Particularly WESTMAN's extensive and thorough experimental studies on animals have furnished evidence that the diencephalon, the pituitary and the genital organs are intimately related to one another. The investigations of WESTMAN and collaborators into the metabolism in the pituitary and diencephalon also seem to suggest that metropathia haemorrhagica cystica and changes in the different parts of the brain stem might be correlated. Our experience at Radiumhemmet has shown that the psychic condition of patients suffering from recurrent functional haemorrhage often suggests hypersensitivity of the autonomic nervous system. According to SJÖBRING's working hypothesis the majority of these patients have a »subvalid» psychic constitution. This author applies the term

»subvalid» to individuals, who have less brain energy than ordinary individuals. The subvalid individual — according to SJÖBRING — is quiet, warry, fastidious, industrious, high-strung, and irresolute.

According to our experience it is important to take this factor into account in the treatment of abnormal functional haemorrhage. This applies also to radiotherapy, where the psychic constitution of the patient is often not sufficiently seriously considered. Nowadays, surgical castration or sterilization by roentgen rays or radium does not present any difficulty. It is, fundamentally important to give serious consideration to the general condition of the patient before instituting radiotherapy, and apart from the local disorder, try to correct the other possible derangements. For this purpose the patient should be subjected to a thorough medical and gynaecological survey, which should include the examination of the extragenital organs giving also serious consideration to the patient's psyche.

The indications for radiotherapy in preclimacteric and climacteric functional haemorrhage should be assessed with careful discrimination irrespective of whether there is evidence of a myoma or not. The younger the patient the greater the need for critical consideration of the indications. The only conclusive indication for radiotherapy is haemorrhage, which notably affects the general condition or the working capacity of the patient, and which fails to respond to less drastic measures than radiotherapy. The psyche of the patients and the risk of serious menopausal symptoms should be given careful consideration. Patients, whose psychic condition is unbalanced, are rarely fit for radiotherapy.

The main purpose of radiotherapy in functional uterine haemorrhage is to introduce menopause in a given case. In Germany, it was popular to attempt the restoration of the normal cycle by the so-called temporary sterilization treatment. This therapy is based on experimental and histological observations on the different degree of radiosensitivity of the ovarian follicles at different stages in their development. Although these observations are certainly well founded, experience has shown that temporary sterilization therapy does not yield any results, which compare to those reported by SEITZ and WINTZ, GAUSS, and others. There may be two reasons for this. First, it is difficult to determine the size of the dose, which should be administered in a given case, and secondly, it is rather doubtful whether the ovary, which represents an organ whose biological functions vary widely, really shows a constant radiosensitivity. This substantiates the importance of a careful and dispassionate evaluation of the indications, although irradiation therapy, which is easily administered and harmless, may be extremely tempting. It does happen fairly often that the surgeon remits a patient for sterilization therapy to the radiologist despite the fact that she suffers from benign

haemorrhage, which does not notably limit her working capacity. The patient may have been subjected to curettage on one occasion, which did not have the desired effect, and the surgeon, therefore advises irradiation therapy. The task of critically evaluating the indications stated, then falls on the radiologist. In many cases favourable results are obtained with less drastic therapeutic procedures than radiotherapy. Often it will suffice to allay the patient's anxiety and to show genuine interest in her complaints. According to our experience, sterilization therapy on the basis of indications, which are not definitely conclusive, does often not yield the desired results from the standpoint of the patient. Admittedly, it stops haemorrhage but nervous and psychic troubles may come on, which may be more troublesome to the patient than the haemorrhage for which she sought medical advice.

If the radiotherapist decides to give irradiation therapy, it is of major importance, to inform the patient in a given case not only of its purpose, but also of the menopausal symptoms.

It has been definitely established that the menopausal symptoms are due to dysfunction of the endocrine glands. As early as 1923, HEYMAN reported the observation that patients, who were sterilized at a comparatively young age subsequent to the treatment of a malignant tumour of the genital organs, developed menopausal symptoms several years later at the age of between 40 and 50 years. This observation supports the assumption that apart from the cessation of the normal ovarian cycle other factors are also concerned in the menopausal symtoms. Just as the endocrine background of the menopausal symptoms has been definitely proved it is equally certain that psychic factors have a bearing on their clinical significance. According to our experience, the radiologist is therefore to be blamed if he omits to inform the patient of the menopausal symptoms, which she may develop after the cessation of the menstrual cycle. Out of 52 patients, who were treated by irradiation and had not been informed of these facts before the institution of irradiation therapy, 27 (51.9 per cent) were suffering from more or less troublesome menopausal symptoms, whereas out of 168 patients, who were treated by irradiation over the same period of time, and who were properly informed before they were subjected to this treatment 126 (75 per cent) did not suffer from menopausal symptoms.

As regards the indications for radiotherapy in preclimacteric haemorrhage the following point is particularly important: Radiotherapy should not be given unless a malignant tumour of the genital organs can be definitely ruled out. Menorrhagia does not exclude this possibility. Unfortunately, cases are sometimes met with, where this possibility has not been seriously considered. The radiotherapist is then to be blamed, and not the physician, who remits the patient for radiotherapy. The

radiotherapist should make it a point to send the patient, who was not sufficiently carefully examined, back to her physician for another thorough medical and gynaecological survey. As has been mentioned before, the general examination of the patient is incomplete unless it includes intra-uterine exploration and curettage.

Other important points worthy of mention in this connection are the following: Persistence or recurrence of irregular haemorrhage following radiotherapy in doses, which — according to the experience of the radiologist — should have a beneficial effect, are symptoms, which definitely point to the fact that the indications for radiotherapy were not conclusive. As a rule, patients of this type should not be given another course of irradiation treatment. They should be followed up as carefully as possible and operated upon on the slightest suspicion of an ovarian tumour, a submucous myoma or neoplasm of the uterus. Experience has shown that more or less malignant ovarian tumours, which are difficult to detect, are fairly often present in cases of this type.

Roentgen treatment given to the ovaries on anterior and posterior fields, and intra-uterine application of radium tubes are the main radiologic procedures resorted to for therapeutic purposes. The historical background of sterilization therapy by roentgen rays is very interesting mainly owing to the fact that the problem of dosimetry, particularly between the years 1910 and 1930, has been intimately linked up with the investigations into the effect of roentgen rays upon the ovary and its cellular compoents. The physiological and biological factors determining sterilization are exhaustively discussed in text-books of gynecology (VEIT-STÖCKEL, HALBAN-SEITZ, and others). Particularly SEITZ and WINTZ, KRÖNIG, FRIEDRICH, and GAUSS hold that a dose of 280 r given to the ovary (34 per cent of a skin erythema dose) in a woman at the age between 40 and 50 years invariably brings about permanent sterilization. Most radiotherapists have advanced the view that the effect of roentgen rays upon abnormal functional haemorrhage is mediated through the ovaries. Only French authors (BÉCLÈRE), attribute importance to an effect also upon the uterus. Most publications on radiotherapy in climacteric haemorrhage revolve around the sterilization dose stated above (»Kastrationsdosis» according to SEITZ and WINTZ, »Ovarialdosis» according to KRÖNIG and FRIEDRICH). It does not seem probable that the ovary, whose biological function varies widely, would show the same radiosensitivity in different phases of its functional cycle and in different patients.

As regards intra-uterine radium treatment one gains the impression that most radiotherapists concentrate their efforts on giving to the ovary a dose, which is sufficiently large to bring about sterilization, and that they determine the quantity of active element and the length of the

irradiation time on that basis. The view has also been advanced tha radium treatment has some effect upon the endometrium, and that th vegetative and trophic menopausal symptoms are less troublesome afte intra-uterine radium application than after roentgen treatment. Th objection, however, must be raised against these statements that ther is no possibility of grading the menopausal symptoms in a scientificall adequate manner, and that the clinical observations may readily b suggestively influenced.

The technique employed varies widely in different hospitals. Most radiotherapists use for intra-uterine therapy 50—100 mg. Ra-element. Brass, silver, lead, platinum or gold are used as filters in thicknesses, which give a filtration corresponding to that of 1, 2 or 3 mm. lead. The length of the irradiation time varies considerably. Most radiotherapists report to have obtained satisfactory results with 1,200—3,000 mg-hours in 95—100 per cent of the cases. HURDEN, SCHMITZ and BUNDY, KEENE and PAYNE, use 600—1,200 mg-hours with a filtration of 1 mm.—2 mm. brass. HALTER uses 900 mg-hours with a filtration of 0.6 mm. silver. Also STACY and MUSSEY, and GÀL recommend a relatively small dose. They give approximately 700 mg-hours or less, and repeat the treatment if the first course was unsuccessful. STACY gave a second course of intra-uterine radium application only in 14 out of 263 patients treated for abnormal functional bleeding.

Since FORSSELL began sucessfully to treat cases of abnormal functional bleeding and myoma at Radiumhemmet we approached the therapeutic problem along a different line than that stated above. In the beginning at Radiumhemmet, FORSSELL suggested that the treatment as far as possible should be conformed to individual requirements and recommended the application of small roentgen or radium doses. He advised repeating the treatment, if necessary, giving special consideration to the clinical course in a given case. This technique was rather difficult to apply because profuse haemorrhage may come on during the treatment.

On the basis of our experience Radiumhemmet uses the following standard technique in the treatment of preclimacteric uterine haemorrhage. Satisfactory results have been obtained in 96—100 per cent of the cases. *Roentgen treatment applied to the ovaries:* Two anterior fields: 75 cm². Compression: 40 cm. focus-skin distance. One posterior field: 175 cm²; 40—50 cm. focus-skin distance, 175 kv. 15 milliampère. Filter: 0.5 mm. Cu and 1 mm. Al. Skin dose: 650 r-units. One irradiation on each field and one treatment per day.

Intra-uterine radium treatment: 40 mg. radium element in four radium tubes, each tube measuring approximately 11 mm. in length. Filter: 0.35 mm. gold, and 0.3 mm. platinum equivalent to a filtration of 1.1 mm.

le d for hardest irradiation with γ-rays. Irradiation time: 16 hours (640 m -hours).

At Radiumhemmet Heyman has long been recommending intrauterine ra ium application preferably to roentgen treatment for the following re sons.

1st Radium can and should be applied immediately after curettage. The treatment does not cause any serious discomfort to the patient and does not necessitate a prolonged stay in hospital.

2nd A lesser amount of normal tissue is irradiated by radium than by roentgen rays.

3rd The effect of intrauterine radium treatment upon haemorrhage is more rapid, occasionally it may even be immediate.

As a rule, it is not difficult to determine at the time of curettage whether a malignant growth is present or not. Should the microscopic examination of the curettings reveal the presence of a malignant tumour the radium treatment given previously need not be taken into account in the treatment of the tumour.

Intra-uterine radium treatment is contraindicated if the patient gives a history of an infectious process in the adnexa. Out of more than 400 patients, who received intra-uterine radium application at Radiumhemmet, salpingitis came on in only two after this treatment. Other complications did not occur, neither did the patients complain of any other troubles either in connection with the treatment or after it.

At Radiumhemmet 1913—1945 altogether 772 patients were examined for preclimacteric or climacteric haemorrhage. They were sent to us from other hospitals or from gynaecologists for irradiation treatment. To 168 of these patients no irradiation treatment was given, either because the indications were not absolutely convincing or because there was a risk of severe menopausal symptoms coming on. In this connection it is worthy of mention that five patients of the last mentioned group were later given sterilization treatment by roentgen rays in another hospital and developed menopausal symptoms, which incapacitated them for work.

A detail discussion of the individual clinical symptoms and the results obtained with radiotherapy would be too exhaustive for the scope of this contribution. A paper is in preparation, in which the cases under study will be reported and discussed in detail. Here, I only wish to state that excellent results were obtained with both intra-uterine radium application and roentgen therapy, and that the effect of radium treatment was more rapid than that of roentgen therapy.

In 1934, I reviewed the cases of preclimacteric and climacteric haemorrhage treated up to that year. On this occasion it was found that the

patients to whom intra-uterine radium treatment had been given developed characteristic menopausal symptoms causing comparatively little discomfort, several months or years after haemorrhage had stopped whereas in the patients treated by roentgen rays, these symptoms became manifest shortly after the menopause, and were often troublesome. The present study of these cases verified this observation. Out of 772 patients, 770 were either reexamined on several occasions at Radiumhemmet by me or information as to their condition was obtained by questionnaires or by making personal inquiries in their homes. In order to obtain reliable information also about the patients, who were no longer alive when this investigation was made, the records on these symptoms filed either in the archives of hospitals or private surgeries were carefully reviewed or, inquiries were made with their relatives.

The difference in time when menopausal symptoms became manifest after radium irradiation and after treatment by roentgen rays in cases observed at Radiumhemmet, has not yet been dealt with in the literature. Since this clinical observation cannot be influenced by suggestive factors this difference in time might perhaps be due to the fact that a comparatively small radium dose is used at Radiumhemmet, and that compared to roentgen therapy a higher degree of ovarian incretory activity — which is of primary importance to the psychic condition and physical constitution of the patient — is maintained after intra-uterine radium application. The clarification of this problem is practically, clinically and theoretically of major importance. In extensive studies (1938—1946) at Radiumhemmet this problem was approached along the following lines.

1st Microscopical examination of the ovaries in patients operated upon after having received intra-uterine radium application for preclimacteric functional haemorrhage.

2nd Comparison of the dose distribution over the ovary with roentgen irradiation to the dose distribution with intra-uterine radium application.

3rd Examination of urinary excretion of gonadotropic follicle-stimulating hormone in patients treated by radium or roentgen.

4th Examination of the urinary excretion of oestrogenic hormone in these patients.

5th Examination of the degree of response of the endometrium to oestrogenic hormone in patients treated by radium or roentgen rays.

6th Examination of the effect of radium irradiation applied to one uterine cornu in rabbits. Comparison between the effect of roentgen rays and radium upon the uterus, ovaries, and pituitary in rabbits.

1. Microscopical Examination of the Ovaries in Cases Operated upon after having received Intra-uterine Radium Application for Preclimacteric Functional Haemorrhage

As a rule there are no indications for surgical treatment in patients having received radiotherapy for regular or irregular functional bleedings. In five patients a laparotomy was performed after intrauterine radium treatment because of a submucous myoma or an ovarian tumour. In two of these five patients corpora lutea were found in the ovaries, suggesting that the ovaries were still in function.

2. Comparative Studies of the Dose Distribution over the Ovary with Roentgen Irradiation and Intra-uterine Radium Application

a. Determination of the Dose delivered to the Ovary by Roentgen Irradiation

The determination of the position of the ovary in relation to the anterior abdominal wall and the back presents difficulty in the living human being. In order to get an idea whether it is possible to use the ordinary tables of depths doses in determining the ovarian dose, I made direct measurement on the ovary at the time of roentgen irradiation after laparotomy. QUIMBY made similar measurements in connection with post-mortem examinations.

After having thoroughly discussed the purpose of my experiments with a patient suffering from a pathology of the genital organs, which required surgical treatment, and obtained her permission to make it, I proceeded in each case as follows: I performed laparotomy, cleared up the pathology, and fixed, at the end of the operation, two Sievert ionization chambers on each ovary, sutured the abdominal wall, and deflated as far as possible the air with the aid of an air pump. Subsequent to the exposure of the ovary to roentgen irradiation according to the routine technique I made a second laparotomy and removed the chambers. Under these experimental conditions one ovary was subjected to roentgen irradiation in eight patients by irradiating one of two abdominal fields, whereas in six a central dorsal field was irradiated. I used a technique, which conformed to the standard methods with the exception of the dose, which was smaller. The dose delivered to the ovary varies of course in conformity with the position of the ovary and fat distribution in a given case. As may be seen from the Table 1 the individual variations are comparatively small when irradiating one of two abdominal fields, particularly if the fact is taken into consideration that physically the method of determination is in itself subject to some margin of error.

Table 1.

Intensities in r-units with roentgen rays to the ovaries on one of two anterior fields. Compression. Fields: 75 cm². 170—175 kv. 15—20 milliampère. Filtration: Cu 0,5 mm. + Al 1 mm. Focus-skin distance: 40 cm.

Intensity to the skin in r	Intensities to the ovaries	
	irradiated side	non-irradiated side
278 r	127 r 46 %	34 r 12 %
422 r	219 r 52 % 256 r 61 %	46 r 11 %
398 r	208 r 52 % 240 r 60 %	21 r 5 %
400 r	222 r 56 %	49 r 12 %
410 r	210 r 51 %	46 r 11 %
398 r	261 r 67 %	42 r 11 %
285 r	148 r 52 %	31 r 11 %
391 r	199 r 51 %	43 r 11 %

Table 2.

Intensities in r-units with roentgen rays to the ovaries on one posterior field (175 cm²—200 cm²). 165—170 kv. 15 milliampère. Filtration: Cu 0,5 mm. + Al 1 mm. Focus-skin distance: 40—50 cm.

Intensity to the skin in r.	Focus-skin distance	Intensities to the ovaries in r.
405 r	40 cm.	89 r = 22 per cent 105 r = 25 per cent
418 r	40 cm.	96 r = 23 per cent 88 r = 21 per cent
398 r	40 cm.	95 r = 24 per cent 103 r = 26 per cent
400 r	40 cm.	76 r = 19 per cent 88 r = 22 per cent
389 r	50 cm.	133 r = 34 per cent 122 r = 31 per cent
438 r	50 cm.	63 r = 14 per cent 63 r = 14 per cent

On an average, about 54 per cent of the skin dose is delivered to the ovary, which is irradiated. Although the beam of roentgen rays is directed at right angles towards the skin, approximately 11 per cent of the skin dose is delivered to the non-irradiated ovary through secondary irradiation effect (see Table 1). SEITZ and WINTZ seem to have overlooked this fact when determining the sterilization dose. When irradiating a dorsal field the individual variations are greater. The dose delivered to the ovary is then on an average 23 per cent of the skin dose (Table 2).

The reason for administering 650 r is stated in the section of this paper dealing with the technique by which roentgen therapy is applied at Radiumhemmet in the treatment of functional haemorrhage (pages 742—743). We have deliberately given smaller skin doses (approximately 500 r) to some patients, but their effect upon haemorrhage is not nearly so satisfactory. If each field is exposed to 650 r it may reasonably be assumed — taking the time factor into consideration (treatment time three days) — that a dose of 350—400 r, which corresponds to an intensity rate of 12 r/min. given to the ovary should be efficacious.

b. Determination of the Dose delivered to the Ovary by Intra-uterine Radium Application

In five patients the attempt was made directly to measure the dose distribution over the ovary. Radium was inserted into the uterine cavity before operation, and after opening of the abdomen the Sievert ionization chambers were fixed on the ovary and left in place for an adequate period

Table 3.

Intensities to different points on one ovary with intra-uterine radium treatment of climacteric functional haemorrhage. Four radium tubes in tandem. Filtration equivalent to one mm. lead. About 40 mg. Ra. element. Irradiation time: 16 hours (640 mg-hours). The measurements were made at the time of laparotomies. One Imc. hour × 8 = 8 r-units. In two patients the measurements are made on both ovaries (A. L. A., H. H.).

Case	Intensities to the ovaries	
	Intensity millicurie = Imc.	r-units
A. L. A.	2.5 Imc.	320 r.
	1.6 Imc.	205 r.
	1.6 Imc.	205 r.
	1.4 Imc.	179 r.
H. H.	3.9 Imc.	499 r.
	2.5 Imc.	320 r.
	3.4 Imc.	435 r.
	2.2 Imc.	282 r.
E. A. N.	1.6 Imc.	205 r.
	1.0 Imc.	128 r.
E. K. L.	0.9 Imc.	113 r.
	0.7 Imc.	90 r.
S. A.	2.2 Imc.	282 r.
	1.8 Imc.	230 r.
	1.3 Imc.	166 r.

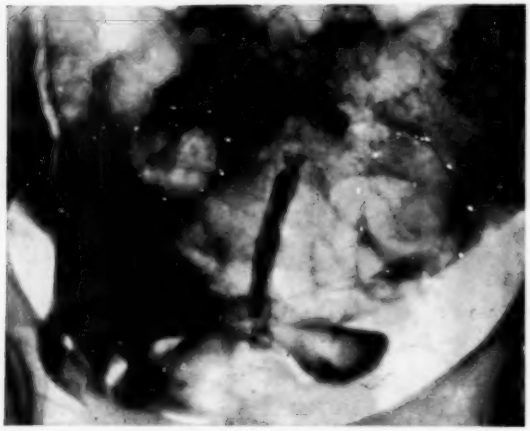

Fig. 1. Roentgenogram (pelveography) shoving the distance between the ovaries and the radiumtubes in the uterine cavity.

of time. There are great variations in individual cases because the distance between the position of the chambers on different parts of the surface of the ovary and the radium element varies widely. But also in other respects the variations are so great that it seems to me not easy to attribute importance to these measurements in determining the dose distribution over the ovary with intra-uterine radium application (see Table 3). Besides, it is questionable whether the position of the ovaries as identified at laparotomy and the post-mortem examination really corresponds to their physiological position in the non-anaesthesized individual. According to text-books of Anatomy and to MARTIUS the shortest distance between the uterine cavity and ovary is 4.5 cm.—5.5 cm. The measurements I made at the time of numerous operations or post-mortem examinations verified these data. WESTMAN, however, demonstrated that the ovary changes its position considerably, and twists itself along its longitudinal axis under normal conditions in both the human being and animals. Bearing in mind that both the ligamentum latum and ligamentum suspensorium ovari contain streaks of smooth muscles this distance between the ovary and the uterus does probably not correspond to physiological conditions. In the attempt to determine the position of the ovary and the dose delivered to it, I studied these conditions in collaboration with R. KJELLBERG with the aid of pelveography in 28 patients. Diluted perabrodil, approximately 150 to 175 cc. were intraperitoneally injected with the aid of a needle, which was inserted into the Douglas cul-de-sac through the posterior fornix. Similar methods of examinations were described by MOLINENGO and CONTE. The injection does not cause any discomfort to the patient. With the exception of one case, where perabrodil was injected into the parametrium, the contrast medium was ministered peritoneally. We deliberately refrained from making hysterosalpingography because experiments have shown that irritation of the fallopian tubes causes displacement of the ovary. By taking different

views of the pelvis we were able to measure on the film the shortest distance between the ovary and either an instrument or the radium element inserted into the uterine cavity. This distance measured between 2.6 cm and 4.4 cm. In 27 patients it measured on an average 3.25 cm. The size of the ovary itself varies widely. In women at the preclimacteric age it is estimated to measure at least roughly $3 \times 2 \times 2$ cm. The difference between this on roentgen-films measured distance and the distance established in post-mortem examinations is not great. Considering the circumstance that ovaries and uterus are organs in the pelvis depending on each other the difference is comparatively significant.

On the basis of these anatomic determinations, which were made with the aid of roentgen examination and measurements on a paraffin model, we were able to gain an idea of the dose distribution over the ovary with intra-uterine radium application. A uterus constructed of paraffin with a cavity in its center designed for the application of the radium tubes was used as phantom (Fig. 2). The intensity rate was measured with the aid of Sievert ionization chambers and expressed in terms of international millicurie (Imc.). The dose administered to the individual case was calculated by multiplying Imc. by the length of the irradiation time and expressed in Imc-hours. It has not yet been definitely established whether a comparison between the dose expressed in terms of Imc-hours delivered by γ-rays and the dose expressed in r delivered by roentgen rays is permissible. Numerous authors have tackled this problem, and computed physically a conversion coefficient by means of which the dose expressed in Imc-hours can be referred to r though difference in irradiation must, of course, be taken into account. At Radiumhemmet the figure 8 is used as conversion coefficient, which corresponds to that reported by other physicists. In the tables appended to this paper, the dose, which was either mathematically computed or measured with the aid of ionization chambers on the phantom, is indicated in r. Whether this conversion coefficient, which was physically computed, can be used also for biological experiments is still uncertain. HOLTHUSEN and HAMANN, and STRANDQUIST among others exposed the skin to γ-rays and roentgen rays, and determined the intensity rate on the basis of the skin reaction. These authors feel that the conversion coefficient 8 does not hold for biological experiments and assume that it is less than 8. It is beyond the scope of this paper to investigate whether this assumption is justified. I wish to point out, however, that the doses expressed in r delivered by intra-uterine radium application are probably too large from a biological point of view compared to the dose administered by roentgen rays. Table 4 and Fig. 2 show, however, that the dose delivered by radium to the ovary, which was physically computed, must be smaller

Table 4.

Intensities delivered from four radium tubes in tandem in a small rubber container. About 40 mg. Ra. element. Filtration equivalent to one mm. lead. Irradiation time: 16 hours (640 mg-hours). One Imc. hour × 8 = 8 r units.

12 mm.	14 mm.	14 mm.	12 mm.	The radium container with four radium-tubes in tandem.
	2,513 r.	2,381 r.		1,293 r.
	10 mm.			
	1,101 r.	1,024 r.		717 r.
	570 r.	546 r.		447 r.
	407 r.	381 r.		298 r.
	251 r.	248 r.		225 r.
	177 r.	173 r.		160 r.
	a	*b*	*c*	

a. The numbers on the vertical line *a* correspond to the intensities in cm:s from the centrum of the radiumcontainer.

c. The numbers on the vertical line *c* correspond to the intensities in cm:s from the end of the radiumcontainer.

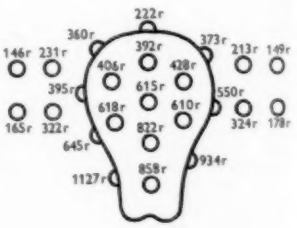

Fig. 2. Diagram showing the intensities to the outside of the uterus (paraffin phantom). Intrauterine treatment with four radium tubes in tandem. 64 mg. Ra.-element. Filtration equivalent to one mm. lead. Irradiation time: 10 hours (640 mg-hours).

than the dose delivered by roentgen rays, at least in extensive parts of this organ. The dose delivered by roentgen rays to the ovaries in using the standard technique (skin dose: 650 r) is 350—400 r. If we used a smaller skin dose (approximately 500 r) the effect upon haemorrhage was not nearly so satisfactory as in patients treated with the standard technique. The dose delivered by radium to the ovary is in extensive parts of this organ 250 to 150 r. The difference between the dose delivered by roentgen rays and that by radium to the ovary is obvious. Besides, for the roentgen experiments on the ovary an intensity rate of 12 r/min. was employed, whereas for the experiments with intra-uterine radium application an intensity rate of only 0.4—0.15 r/min. was used. Experiments on the drosophila, algae, and so forth have demonstrated

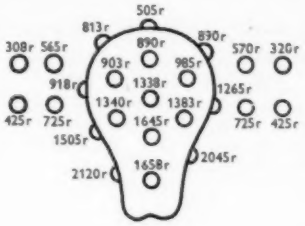

Fig. 3. Diagram showing the intensities to the outside of the uterus (paraffin phantom). Intra-uterine treatment with four radium tubes in tandem. 64 mg. Ra.-element. Filtration equivalent to 3 mm. lead. Irradiation time: 25 hours (1,600 mg-hours).

that the biological effect upon the living tissue is considerably reduced with intensities lower than 5 r/min. than with higher intensities.

The investigations reported in this paper furnish convincing evidence in support of the assumption that the biological effect upon the ovary must be considerably smaller with intra-uterine radium application than with roentgen treatment.

In this connection it should be mentioned that with intra-uterine radium application only 650 mg-hours with a filtration equivalent to 1 mm. lead are used at Radiumhemmet. *Our experience has shown that patients treated with this dose often do not manifest menopausal symptoms until fairly long after the cessation of haemorrhage.* Many radiotherapists generally use considerably larger doses and claim that the menopausal symptoms are milder after intra-uterine radium application than after roentgen therapy. It may be difficult to estimate the value of such an observation. We have so far no possibility of grading the menopausal symptoms in a scientifically adequate manner. Fig. 3 shows that the dose delivered to the ovary is considerably larger than that given to the patients treated at Radiumhemmet if, for instance, 64 mg. Ra-element are intra-uterinely applied over a period of twenty-five hours using a filtration equivalent to 3 mm. lead.

3. Comparative Studies of the Urinary Excretion of Gonadotropic Follicle-stimulating Hormone in Patients treated by Radium and Roentgen Rays

In the attempt to furnish biological evidence in support of the clinical observation of the relative difference in time when menopausal symptoms become manifest after intra-uterine radium application and roentgen treatment I determined the urinary excretion of gonadotropic hormone on 48 patients treated by radium and on 35 treated by roentgen making serial determinations in each case. ZONDEK, and a short time later, FLUHMAN demonstrated that the quantity of follicle-stimulating gonadotropic hormone in the urine and blood increases after surgical removal of

Table 5.

Urinary excretion of follicle-stimulating gonadotropic hormone in patients at the normal menopause.

Follicle-stimulating hormone in one liter of urine.

Duration of menopause in years:	< 40 mouse units	> 40 < 80 mouse units	> 80 mouse units
1		2	9
1 —1½			6
1½—2			5
2 —3		2	6
3 —4			5
4 —7	1	1	7
7	1	2	10

64 tests for follicle-stimulating hormone in the urine were made on 57 patients. In 48 patients > 80 mouse units (84.2 per cent) were found in one liter of urine, in 11 > 165 mouse units in one liter of urine.

14 of the 57 patients had slight menopausal symptoms, 37 patients moderate menopausal symptoms and 6 patients severe menopausal symptoms.

the ovaries in women at the reproductive age. Also in patients sterilized by roentgen rays and in women at the normal menopause, ZONDEK found that urinary excretion of prolan A was occasionally (in 25 per cent of the cases) >110 mouse units in one liter of urine. His observation, however, is based on only one determination in the individual cases. HAMBURGER, SAETHRE, OESTERREICHER and others, made serial examinations in individual cases and demonstrated that urinary excretion of gonadotropic follicle-stimulating hormone increases in nearly all women at the normal menopause. These findings, however, may vary widely on different occasions, and therefore it is necessary to test the urine for this hormone several times in a given case.

The threshold values for the quantities of follicle-stimulating hormone, which are physiologically excreted in women at the reproductive age, are not yet definitely established. Excretion of >80 mouse units in one liter of urine, however, should be considered as a pathological value. In discussing menopause and the effect of radiation treatment upon the function of the ovaries I therefore consider an excretion of >80 mouse units as a sign definitely indicating that the function of the ovaries is considerably lowered. In 57 patients, who had been at the menopause for between < one year and > 7 years, and who had not been treated either radiologically or surgically, 64 determinations of the urinary excretion of follicle-stimulating hormone were made. Table 5 shows that out of 57 patients, >80 mouse units in one liter of urine were demonstrated in 48. I feel convinced that this quantity of follicle-stimulating

Table 6.

Comparative study on patients treated with radium and roentgen rays with special consideration of the lapse of time when follicle-stimulating hormone appears in the urine after treatment.

> 80 mouse units folliclestimulating hormone in sample of urine collected over 24 hours.	> 80 units of follicle-stimulating hormone									
	at the time of treatment	after months				after years				absent
		2	4	6	12	2	3	4	5	
Number of cases treated by radium	4	2	3	—	6	17	5	4	3	4
Number of cases treated by roentgen rays.		20	13	2						

> 165 mouse units follicle-stimulating hormone in sample of urine collected over 24 hours.	> 165 units of follicle-stimulating hormone									
	at the time of treatment	after months				after years				absent
		2	4	6	12	2	3	4	5	
Number of cases treated by radium	1	2	2	—	2	7	7	2	1	23
Number of cases treated by roentgen rays.		7	9	5	6	4				4

hormone would have been found in all these patients if an adequate number of tests for this hormone had been made in the individual cases.

In 48 patients who had received intra-uterine radium application 1,038 tests for the urinary excretion of follicle-stimulating hormone were made, and in 35 treated by roentgen rays, 427. The indications for radiotherapy were abnormal haemorrhage conforming to either menorrhagia or metrorrhagia. In all cases who had received intra-uterine radium application the results were fully satisfactory. To some patients treated by roentgen rays a smaller dose than that employed with the standard methods was deliberately administered. In the case of these patients haemorrhage recurred. Nevertheless, > 80 mouse units follicle-stimulating hormone were excreted in one liter of urine during the periods of amenorrhea. Considering that the patients suffering from abnormal uterine haemorrhage in this series were at the climacteric or preclimacteric age, and that several of the patients treated by intra-uterine radium application were aged approximately 50, it is not surprising that the urinary excretion of follicle-stimulating hormone increased shortly after treatment in some patients, who had been subjected to radium therapy.

The table 6 offers definite evidence for the considerable difference in time when the follicle-stimulating hormone appears in the urine after intra-uterine radium application and roentgen treatment. This strongly supports the clinical observation that a higher degree of ovarian function is maintained after treatment by intra-uterine radium application than by roentgen rays.

4. Comparative Studies of the Urinary Oestrogenic Excretion in Patients treated by Intra-uterine Radium Application and Roentgen Rays

Our knowledge of the correlation between the function of the ovaries and the content of oestrogenic hormone of the blood and urine is still incomplete. Literature abounds in investigations into this problem, but the value of a good many of them is reduced by the fact that they were made to determine only free oestrogen. The fact that the oestrogenic hormones are also produced extragenitally, mainly by the cortex of the suprarenal glands, is another factor increasing the difficulty of determining the function of the ovary with the aid of urinary tests for this hormone. Technical difficulties and sources of error of the biological tests for oestrogenic hormones have a bearing upon the results. Serial tests for the content of oestrogenic hormone of the urine by the methods of SMITH and SMITH, ZONDEK, ALLEN and DOISY, were made in 40 patients treated by intra-uterine radium application and in 12 treated by roentgen rays. All these patients were systematically controlled by tests for the content of gonadotropic hormone of the urine. 20 mouse units oestrogenic hormone in one liter of urine were established as threshold value. From Table 7 it may be seen that 20 mouse units or more in one liter of urine were demonstrated on one or several occasion in 29 out of 40 patients (75.5 per cent) treated by radium, and in 4 out of 12 (33.3 per cent) treated by roentgen rays. Rather considerable variations in the quantity of oestrogenic hormone excreted in the urine were observed not only in the individual patient but also in different patients. In the group of patients treated by radium >100 mouse units of oestrogenic hormone in one liter of urine were occasionally found. A careful study of the individual cases shows that the difference between the patients treated by radium and those treated by roentgen is considerably greater

Table 7.

Urinary excretion of oestrogenic hormone in patients treated for climacteric functional uterine haemorrhage by roentgen rays or radium.

Treatment	Oestrogenic hormone in 1 liter of urine.			
	< 20 mouse units		> 20 mouse units	
	Number of cases	Per cent	Number of cases	Per cent
Radium (intra-uterine application)	11	27.5	29	72.5
Roentgen rays	8	66.7	4	33.3

th n Table 7 shows. This also furnishes strong evidence in support of th observation that a considerably higher degree of ovarian activity is m intained in patients treated by radium than in those subjected to ro ntgen rays.

On the basis of 1st, clinical observations, 2nd, studies of the dose distribu on over the ovary, 3rd, determinations of urinary excretion of gonadotro ic follicle-stimulating hormone and oestrogenic hormone, the conclusion see s justified that a considerably higher degree of ovarian activity is maintai ed in patients successfully treated by intra-uterine radium application tha in patients submitted to roentgen treatment.

5. Examination of the Degree of Response of the Endometrium to Oestrogenic Hormone in Patients treated by Radium or Roentgen Rays

What are the reasons haemorrhage ceases in patients treated by radium despite the fact that a considerably higher degree of ovarian incretory activity is maintained than in patients treated by roentgen rays? The explanation of the effect must be looked for in the effect of the radium rays upon the uterus. The histological examination of uteri from patients, who received intra-uterine radium application in the treatment of functional haemorrhage or myoma, does not reveal any changes, which might be definitely referred to the effect of this treatment. This has been reported by several researchers, in Sweden, for instance, by LUNDQVIST, MÖLLER and ESSEN-MÖLLER. The appearance of the endometrium is similar to that of either an atrophic mucosa or a low proliferative mucosa, which does not show any signs of response to hormonal stimulation or, to that of a mucosa showing retrogressive hyperplasia. Admittedly, the vessels often show signs of hyalin degeneration, but these changes occur physiologically also in uteri from women, who have been pregnant. Clinical and experimental investigations (BUSCHBECK, PALMER, KAUFMANN, DAMM, RYDÉN, and others), have demonstrated that an endometrium showing distinct signs of proliferation is not produced unless a certain quantity of oestrogenic hormone is supplied. The production of a proliferative endometrium depends mainly on the following factors: The administration of an adequate quantity of oestrogenic hormone, the length of time, over which it is administered, and adequate administration. Natural oestrogenic hormone given per os has little effect upon the endometrium because 90 per cent are inactivated in the liver (PEDERSEN-BJERGAARD). PALMER showed that 17 mg. synthetic or natural oestrogenic hormone intramuscularly injected over a period of between two and three and a half weeks unfailingly produce a definitely proliferative uterine mucosa in surgically sterilized patients.

With a view to investigating the question whether the threshold value of the effect of the oestrogenic hormone upon the uterine mucosa in patients treated by radium is higher than in patients treated by roentgen rays, 20 patients of the former group and 12 of the latter were given intramuscular injections of natural oestrogenic hormone (dimenformon) or of synthetic hormone (hexestrol) over a period of three weeks. Suction curettage was performed before the introduction of this therapy and five days after its discontinuance. Subsequent to the administration of 20 mg. of oestrogenic hormone the endometrium of all patients treated by roentgen rays showed signs clearly indicating that proliferation was in progress; in places, the glands showed cystic changes, and occasionally there were signs of secretory activity of the glandular epithelium. In 18 patients treated by radium, to whom injections of 20—30 mg. dimenformon or hexestrol were given, curettage yielded only small bits of fibrous mucosa. On the other hand the endometrium of two patients treated by intrauterine radium application showed distinct signs of proliferation after the administration of 35 mg. dimenformon. Considering that there was no noteworthy difference in age, onset of menopause, and so forth between the patients treated by intrauterine application and those treated by roentgen rays, the investigations reported in this paper furnish strong evidence that the favourable results obtained with intra-uterine radium application, as regards both haemorrhage and the maintenance of a higher degree of ovarian function can be referred to the effect of the radium rays upon the endometrium. The threshold value of the effect of oestrogenic hormone upon the endometrium is considerably higher in patients treated by radium than the effect, which it exerts physiologically.

6. Examination of the Effect of Radium Irradiation applied to One Uterine Cornu in Rabbits.

In order to gain an idea of the difference between the effect of intrauterine radium application and roentgen treatment upon the uterus and ovary, the ovaries of 31 rabbits were exposed to roentgen rays on one abdominal field, and in 67 rabbits a radium tube was applied to one cornu of the uterus. The elaboration of a method permitting a satisfactory application of the radium and estimation of the most adequate dose presented great difficulty. Briefly, it may be said that roentgen rays and intra-uterine radium application were given in doses, which considerably exceeded those given in the treatment of preclimacteric functional haemorrhage in the female human being. After irradiation the rabbits were injected with oestrogenic hormones or possibly progesterone over longer or shorter periods, mated before, during and after the endo rine

herapy, carefully controlled and finally killed either by injecting air into he veins or under ether anaesthesia. Biopsies were taken at the time of apatoromy. The genital organs and the pituitary were preserved, eighed, and microscopically examined. A detailed discussion of these udies and of the results obtained is too exhaustive for the scope of his paper. For the better understanding of the effect of intra-uterine adium application the following observations are worthy of consideration.

The ovary corresponding to the non-irradiated cornu was larger and heavier in all animals under study. It contained follicles at different stages of maturation, haemorrhagic spots, and responded with ovulation and corpus luteum formation after copulation. The colour of the ovary corresponding to the cornu irradiated by radium was yellowish-white, and occasionally showed small follicular cysts and, in places haemorrhagic spots. Variations occurred corresponding to the difference in size of the dose given. Several rabbits became pregnant in the cornu of the uterus, which was not directly irradiated. The fetus, however, did not develop normally; it shrivelled up.

The non-irradiated uterine cornu responded normally to the administration of oestrogenic hormone and progesterone. There was marked oestrus response; histologically, there were no morphologic changes demonstrable either in the uterine wall or its vessels.

The cornu of the uterus irradiated by radium was often distended by serous fluid owing to stenosis of the narrow uterine cavity. It either did not respond at all or only weakly to hormonal stimulation. The appearance of the cross-section through the cornu of the uterus was similar to that of the uterus of a castrated rabbit. As a rule, noticeable changes in the epithelium or stroma, which would have been referable to a direct local effect of the radium rays, were not demonstrable. Only in a small number of rabbits did the uterine wall show signs of direct damage in the form of necrobiotic changes. They were partly due to infection. In the remaining cases the appearances of the uterus and epithelium were normal whereas the stroma was often somewhat more dense and fibrous than is the norm. A point worthy of mention is the observation that the arterioles of the irradiated cornu, in contrast to those of the non-irradiated cornu, showed marked signs of a more or less obliterating endarteritis or hyaline degeneration. These types of changes in the arterioles are common in irradiated tissue. As regards the uterine mucosa, however, they may theoretically have a particular interest. The clinical and experimental studies of numerous workers, particularly the investigations of WESTMAN, BARTELMEZ, DARON, HARTMAN, and MARKEE, directed attention to the anatomical and physiological changes in the arterioles and the veins during menstruation

particularly in the arterioles. The observations of MARKEE on endometrial tissue transplanted into the anterior chamber of the eye in monkeys are of special significance. As regards the functional alteration of the arterioles, MARKEE speaks of a »Blushing and blanching phenomenon». MARKEE has proved a correlation between the functional alteration of the arterioles and menstrual bleeding. If these observations are compared to the experiences made at Radiumhemmet and the clinical and experimental observations reported in this paper, it is possible that the effect of radium rays upon uterine bleeding is partly mediated through an effect upon the arterioles.

SUMMARY

Radiotherapy in cases of preclimacteric functional haemorrhage consists either in roentgen irradiation of the ovaries or intra-uterine radium application. Both methods yielded excellent results at Radiumhemmet, Stockholm. At Radiumhemmet 640 mg-hours of radium with a filtration equivalent to 1 mm. lead are given immediately after curettage. Exhaustive, clinical, endocrine and experimental studies, and determinations of the distribution of the dose over the ovary have shown that a considerably higher degree of ovarian function is maintained after intra-uterine radium application than after roentgen therapy though haemorrhage often stops earlier after radium-therapy than after roentgen irradiation. The effect of radium therapy is perhaps partly mediated through its action upon the arterioles in the uterine mucosa. Notwithstanding these observations it is of major importance to assess the indications for radiotherapy with careful discrimination.

ZUSAMMENFASSUNG

Intrauterine Radiumbehandlung oder Röntgenbestrahlungen auf die Ovarien sind die Hauptmethoden bei radiologischer Therapie funktioneller praeklimakterischer Blutungen. Ausgezeichnete Erfolge werden am Radiumhemmet in Stockholm mit diesen Methoden erreicht. In direktem Anschluss an die immer obligatorische Kürettage werden 640 mgr-Stunden Radium intrauterin verabreicht bei Verwendung eines Filters ekvivalent mit dem von 1 mm. Blei. Nach genauen klinischen, endokrinologischen und experimentellen Untersuchungen und nach der Strahlendosisverteilung auf die Ovarien zu urteilen wird die Ovarialfunktion in ganz anderem Masse nach intrauteriner Radiumbehandlung als nach Röntgenbestrahlungen auf die Ovarien erhalten, obgleich die Blutungen oft schneller nach der ersten als nach der letzteren Behandlungstechnik aufhören. Der Effekt der intrauterinen Radiumbehandlung ist teilweise wahrscheinlich die Folge der Strahleneinwirkung auf die Arteriolae des Endometriums. Trotz dieser Wahrnehmungen ist es aber wünschenswert, dass Strahlenbehandlung nur dann verabreicht wird, wenn die praeklimakterischen oder klimakterischen Blutungen den allgemeinen Zustand der Patientin beeinflusst haben.

RÉSUMÉ

Pour l'actinothérapie des métrorragies fonctionnelles avant la ménopause on a recourt soit aux Rayons Roentgen dirigés sur les ovaires, soit au Radium placé à l'intérieur de l'utérus. Au Radiumhemmet, Stockholm, les deux méthodes donnent d'excellents

ésultats. On y applique une dose de 640 mgr/heure à travers un filtre équivalent à mm de plomb, et cela immédiatement après curettage. A en juger par des recherches xactes, cliniques aussi bien qu'endocrinologiques et expérimentales, et par la détermination de la répartition des doses au niveau de l'ovaire, la fonction endocrinienne de ce ernier est conservée à un degré bien plus marqué après le traitement par le Radium qu'après celui par les Rayons Roentgen, bien que les hémorrhagies cessent souvent plus vite après la première technique de traitement qu'après la dernière. L'effet de la radiumthérapie s'obtient probablement en partie par action sur les arterioles de la muqueuse utérine. Malgré ces observations il est cependant nécessaire de poser très sévèrement les indications de l'actinothérapie des métrorragies fonctionnelles.

FROM THE GYNÆCOLOGICAL CLINIC (HEAD: PROF. JAMES HEYMAN) OF THE RADIUMHEMMET, STOCKHOLM

RECTAL INJURIES FOLLOWING THE STOCKHOLM METHOD OF TREATMENT OF CANCER OF THE CERVIX UTERI[1]

by

Axel Ingelman-Sundberg

The purpose of this investigation was to study the pathogenesis of the radium proctitis and its influence upon the cure rate. Therefore the 3,392 cases of cancer of the cervix uteri treated at the Radiumhemmet in 1914—1937 have been analysed. Since 1914 the examination, treatment and follow-up have been executed under the supervision of Prof. HEYMAN. Thus the classification and treatment have been very uniform. Before 1930 we used the original *Stockholm method*, worked out by FORSSELL and HEYMAN in most cases. It is a fractionated brachyradium treatment where the filtration is equivalent to 3 mms. of lead given in a series of 3 treatments. A typical treatment series would be:

In the uterus 40 mg. el. × 20 hrs. = 800 mg. el. hrs.
In the vagina 75 mg. el. × 20 hrs. = 1,500 mg. el. hrs.

The treatment is repeated three times with an interval of a week between the first and second treatment, and three weeks between the second and third. Because of an increasing number of patients there has been a lack of sufficient beds and radium. After 1930 it therefore became necessary to change to two treatments with an interval of three weeks in most cases, the total dose being reduced somewhat and amounting to about 2,200 mg. el. hrs. in the uterus and 4,000 mg. el. hrs. in the vagina. Concerning the technique, the readers are referred to the papers by HEYMAN (5, 6, 7). Since 1929 all patients have had supplementary radiation treatment three weeks after the last radium application. Most cases have been given roentgen treatment, 3 × 1/3 SED or 3 × 400 r skin dose since the introduction of the r unit, to each parametrium from the ab-

[1] Submitted for publication, May 12, 1947.

omen using a compression tube. The other data have generally been: about 170 kV, 7—15 mA, focus skin distance 30—50 cms., field size 50—150 sq.cms. Thoraeus tin filter (0.4 mm. Sn + 0.25 mm. Cu + 1 mm. Al) or ½ mm. Cu + 1 mm. Al. A few cases have also been given the same dose from one or two sacroiliac portals. Some patients have had teleradium treatment instead of roentgen treatment or a combination of both, *i. e.* roentgen to one parametrium and teleradium to the other. The teleradium dose has been in general about 15 gr. hrs. to each parametrium, given with the 3 gr. bomb or the 5 gr. bomb with a cone, the skin dose being max. c. 2,500 r (1, 2).

Among all 3,392 cases treated there have been 313 with a rectal injury (9.2 %). According to our experience the lesions may be classified as follows:

	No of cases	% of all cases treated
Subjective symptoms only	28	0.8
Slight local lesions	178	5.2
Ulceration	91	2.7
Rectovaginal fistulas	16	0.5
	313	*9.2*

However, 5 of the fistulas healed spontaneously, and 2 gradually closed to the extent that the only discomfort experienced by the patients was that gases at times were passed per vaginam.

On the whole radium proctitis causes but slight invalidism. The general condition of the patient, and her capacity for work is only slightly affected in most cases. About 8 % of the patients experience no distress at all. On the other hand 17.5 % have experienced severe symptoms such as haemorrhage from the rectum, poor general condition etc. The severity of the subjective symptoms, and the local findings do not always correspond. Severe tenesmus, and particularly bleeding from the rectum may be observed even where there has been no palpable lesion. On the other hand, pronounced rectal oedema or healed ulcers may be found in patients that have never had any symptoms.

In order to study the pathogenesis of the rectal injury the author has from a clinical viewpoint surveyed the measurements made by SIEVERT in 1932 (9) of the radiation intensity in the rectum by radium treatment of cancer of the uterus. From these measurements the conclusion can be made that when using the modified *Stockholm method* with two treatments the total dose needed for giving a radiation proctitis is about 400 Imc.hrs. This value corresponds to the dose measured when the centers of the condenser chambers have been situated 7 mms. from the mucosa towards the lumen. The dose in the mucosa is correspondingly greater. The chief

cause of the rectal injury is a too intense irradiation of the rectum which is chiefly due to the brachyradium treatment. Other measurements have shown that the irradiation of the rectum by the usual supplementary roentgen treatment given from the abdomen, is probably of minor importance in the development of a rectal injury. If roentgen treatment is also given from sacroiliac portals, however, the rectal roentgen dose is so large that it must be considered to contribute to the rectal injury. Conclusions are similar when teleradium is given instead of roentgen.

In order to investigate the influence of the tumour characteristics, the dosage in mg. el. hrs., the influence of syphilis etc., the author has made a detailed analysis of the 313 cases with a rectal injury and a control series of 313 cases. The latter comprises all patients with cancer of the cervix treated in 1914—1937 whose surnames begin with *A*, *B* or *R* plus so many consecutively from the registration with the surnames beginning with *S* that a total number of 313 was obtained. The patients of this latter material were included only if they had been subjected to a follow-up for at least one year, and showed no signs of a rectal injury.

From these investigations it is concluded that the overdosage in the rectum is caused chiefly by the vaginal radium. The application of the radium in the compact manner afforded by the use of capsule like vaginal applicators especially when they cannot be sufficiently separated produces too great a radiation intensity in the rectum, counted as per weight unit of radium element (9). Therefore flat applicators (boxes) are preferred. It is suggested that the intrauterine dose could be increased in suitable cases, and the vaginal one decreased in the same degree. Unfavourable local conditions, such as a narrow vagina, can contribute to an excessive radium concentration. Conversely, a tumour bulging into the vagina can cause a dispersion of the radium, thus diminishing the radiation intensity in the rectum. Syphilis and advanced age are found to be contributing factors to the development of a rectal injury.

The 5-year cure rate among the rectal injury cases is considerably greater than among the rest of the material (49.5 % ± 2.8 % and 24.0 % ± 0.8 % resp.). This can be explained in the following manner.

Some of the most advanced cases die before having developed any symptoms of rectal injury, thus eluding the statistics.

Cases where the tumour is small usually have a greater cure rate than cases where the tumour is large. As the rectal injury series contains a greater number of small tumours than the rest of the material this has contributed to the greater cure rate.

Furthermore the radium dose administered as per volume unit of tumour has been greater among the rectal injury series than among the other cases. The latter probably being the chief cause of the greater cure rate.

The investigation thus points towards the fact that better results could probably be obtained by an individual treatment taking the size of the tumour into special consideration.

All details, illustrations, and statistics concerning this article have been published by the author (in book form) as a supplement to this journal (8).

SUMMARY

This paper is a concentrate of the Supplement LXIV of the Acta Radiologica. The 3392 cases of carcinoma of the cervix uteri treated according to the *Stockholm method* in 1914—1937 at *Radiumhemmet*, Stockholm have been reviewed. Among them rectal injuries have occurred in 313 cases (9.2 %), and they have generally been slight. The chief cause of the injuries is an overdosage of the radium irradiation to the rectum, *i. e.* more than c. 400 Imc. hrs. (physic. appr. 3300 r) measured with SIEVERT's condenser chambers, the centres of which have been applied about 7 mms. towards the lumen from the surface of the rectal mucosa. Contributing factors have been advanced age and probably luetic infection. The rectal injury cases present a greater cure rate than the rest of the material (49.5 % ± 2.8 %, and 24.0 % ± 0.8 % resp.), which is explained by the following factors.

That some of the most advanced cases die before having developed any symptoms of rectal injury, thus eluding the statistics.

That the cases with rectal injuries in general have smaller tumours than the rest of the material.

That the radium dose administered as per volume unit of tumour has been greater among the rectal injury cases than among the other cases.

There seems also to be a parallellism between the radium dosage per volume unit of tumour and the 5-year cure rate showing a greater cure rate with increasing dosage. Thus better cure rates could probably be obtained by increased individualization of treatment, taking the size of the tumour into special consideration.

ZUSAMMENFASSUNG

Diese Arbeit ist eine Zusammenfassung von Supplement LXIV der Acta Radiologica. Die 3,392 Fälle von Krebs des Cervix uteri, die in den Jahren 1914—1937 im Radiumkrankenhause zu Stockholm nach der Stockholmer Methode behandelt wurden, sind durchgesehen worden. Unter ihnen kamen Rektumschädigungen in 313 Fällen (9.2 %) vor, und zwar waren sie meistens leicht. Die Hauptursache der Verletzungen war Überdosierung von Radiumstrahlen auf das Rektum, d. h. mehr als etwa 400 Imc. hrs. (physikalisch etwa 3,300 r.), mit den Sievert'schen Kondensorkammern gemessen, deren Zentren etwa 7 mm von der Rektalschleimhaut gegen das Lumen zu entfernt eingestellt wurden. Beitragende Faktoren waren hohes Alter und wahrscheinlich luetische Infektion. Die Fälle mit Rektalverletzungen zeigen höhere Heilungszahlen als das übrige Material (49.5 ± 2.8 % bzw. 24.0 ± 0.8 %), was durch folgende Umstände bedingt ist: Dass manche der am weitesten vorgeschrittenen Fälle sterben, ehe Symptome einer Rektalverletzung zur Entwicklung gekommen sind, wodurch sie der Statistik entgehen. Dass die Fälle mit Rektalverletzungen im allgemeinen kleinere Tumoren haben, als das übrige Material. Dass die per Volumeneinheit Tumor verabfolgte Radiumdosis unter den Fällen von Rektalverletzung grösser gewesen ist als unter den übrigen Fällen. Es scheint auch ein Parallelismus zwischen Radiumdosis per Volumeneinheit Tumor und 5jährigem

Heilungsprozentsatz vorzuliegen, indem die Heilungszahl mit steigender Dosierung zunimmt. Es würden sich also durch stärkeres Individualisieren der Behandlung, wobei die Grösse des Tumors besonders berücksichtigt werden muss, wahrscheinlich bessere Heilungszahlen erzielen lassen.

RÉSUMÉ

Cet article est une condensation du Supplément LXIV des Acta Radiologica. Les 3,392 cas de cancer du col de l'utérus traités selon la méthode de Stockholm, de 1914 à 1937, au Radiumhemmet, Stockholm, ont été passés en revue. Sur ce total, des lésions du rectum se sont produites dans 313 cas (9.2 %), et elles ont généralement été légères. Leur cause principale était un surdosage dans l'irradiation rectale, c'est-à-dire que celle-ci dépassait 400 I Mc.-heures environ (estimés à 3,300 r. en termes de physique), mesurés aux chambres d'ionisation de SIEVERT, dont le centre avait été placé dans la lumière du rectum à environ 7 mm de sa muqueuse. L'âge avancé, et probablement l'infection luétique, ont été des conditions aggravantes. Les cas avec lésion rectale montrent une proportion de guérisons plus élevée que le reste du matériel (49.5 % ± 2.8 % et 24.0 % ± 0.8 % respectivement), ce qui s'explique par les facteurs suivants: certains des cas les plus avancés se terminent par la mort avant que ne se soit développé aucun symptôme de lésion rectale, et ils échappent ainsi à la statistique; les cas compliqués de lésion du rectum avaient en général des tumeurs plus petites que les autres dans ce matériel; la dose de radium administrée par unité de volume de la tumeur a été plus grande chez les malades avec lésion rectale que chez les autres. Il semble ainsi y avoir un parallélisme entre la dose de radium par unité de volume de la tumeur et le pourcentage de guérisons après 5 ans, montrant que ce pourcentage augmente avec la grandeur de la dose. Ainsi donc on pourrait probablement obtenir de meilleurs chiffres de guérisons en individualisant davantage le traitement, c'est-à-dire en prenant en particulière considération les dimensions de la tumeur.

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FROM THE RADIOPHYSICAL INSTITUTE OF KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM
(CHIEF: PROF. R. SIEVERT)

A NEW TELERADIUM APPARATUS[1]

by

Sven Benner

In the first teleradium apparatuses, designed by LYSHOLM (1), STENSTRÖM (2) and others, the problem of protecting the staff from the ill effects of radiation was not satisfactorily solved. As the use of teleradium treatment became increasingly common, and as units containing more and more radium were constructed, the need for designs providing better protection became imperative. For this purpose, units had to be designed where the radium could by remote control be removed from the nozzle of the unit to a heavy lead container. The wall thickness of this container should be sufficient to protect the staff effectively when entering the treatment room to change the patients and to direct the unit on the field to be irradiated. Two different units designed by SIEVERT (3) to this end have for many years been in constant use at Radiumhemmet. While representing a considerable advance in comparison to earlier constructions, they have in the course of years been found to have certain disadvantages which made further improvement desirable.

In one of SIEVERT's units, the radium is moved by air pressure from the nozzle of the unit to the protecting container and back through a flexible metal hose. In his other design it is moved by means of a flexible steel ribbon through a rigid metal tube, the opening in the protecting container being closed by a heavy lead shutter after the radium has entered. When reversing the motion, the lead shutter is opened before the radium is pushed down to the treatment nozzle.

As mentioned in SIEVERT's paper (3), the pneumatic apparatus suffers from the drawback that the tube conveying the radium cannot be made flexible enough not to be interfere in the adjustment of the unit to the treatment field[2] and that it is a little noisy in operation. This latter point is more important from the point of view of protection than one might think, for it has been found that the nurse, desiring to avoid any risk of scaring the patient, is apt to neglect moving the radium to the protecting container before entering the room, *e. g.* to check

[1] Submitted for publication, June 30, 1947.

[2] In a design by GRIMMETT (4), this difficulty is considerably reduced.

the adjustment of the unit to a patient who is not lying still. In the course of years the flexible tube many moreover become deformed so that the radium holder occasionally sticks half-way in the tube, heavily irradiating anybody entering the room to remedy the fault.

One disadvantage of SIEVERT's second design is that it operates rather slowly, especially when the position of the unit is such that the heavy, lead-backed radium holder, or the lead shutter, has to be lifted against gravity by the motors of the unit. This, too, results in increased risk of members' of the staff entering the treatment room without waiting for the radium to enter the protecting container and the lead shutter to close, or even without at all turning the switch moving the radium into the protected position. Moreover, the construction is rather complicated, as it contains two motors that must run in the correct succession operated by automatic switches, the proper adjustment of which has been found increasingly difficult as the component parts of the mechanism become worn in the course of years.

In the new design to be described here, these disadvantages have been alleviated or completely overcome. The basic idea is that the movement of the radium holder and the lead shutter should be merged into one continuous movement actuated by one motor, thus increasing the operating speed and simplifying the design. At the same time it was found possible approximately to balance the only heavy moving part remaining, thus avoiding heavy gravitational forces' opposing and slowing down the motion in any position of the unit.

For this purpose, the lead shutter is made in the form of a lead wheel, *A*, revolving around its centre and placed eccentrically inside the large lead protecting container *B*. The latter is movably suspended in a ceiling bracket as in SIEVERT's second design. The radium holder *C* is attached to a steel ribbon wrapped around the circumference. In its protected position, the radium holder fits into a recess in the surface of the lead wheel near the centre of the protecting container *B*.

If the radium is to be moved from the protected position to the nozzle of the unit the wheel is rotated clock-wise. This movement is started by pressing a push-button on a switch-board in the control room. The first part of the revolution carries the radium holder to the upper end of the tube *D*, down which it will then move, pushed by the gradual unwinding of the steel ribbon from the lead wheel. During this period, the plane of the radium holder is parallel to its direction of movement. At the lower end of the tube *D* the radium holder turns through an angle of 90°, stopping with its plane at right angles to the centre line of the nozzle. The lead screen behind the radium need accordingly not be attached to the radium holder to move with this as in SIEVERT's design, which means a considerable reduction in the weight to be transported.

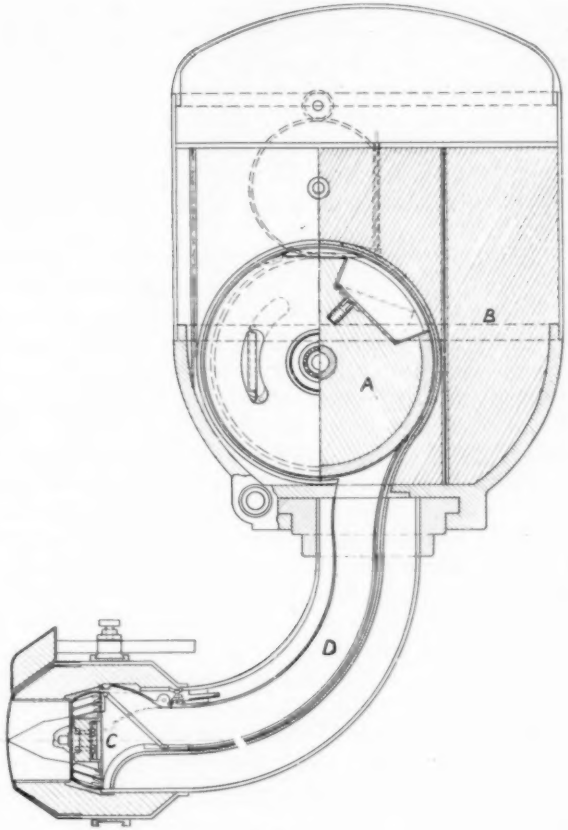

Fig. 1.

When the radium has arrived to its position in the nozzle, the motor stops and a red light on the switch-board indicates that the radium is down. Simultaneously, a synchronous electric clock, whose pointer has previously been set to the desired treatment time, starts running, the pointer moving back towards zero. When it attains this position, a contact is actuated, the clock stops, and the lead wheel begins to run anti-clock-wise. The treatment is thus interrupted by the return of the radium holder to the protected position. When this is reached, another contact is actuated, which stops the motor and lights a green lamp on the switch-board, indicating that it is safe to enter the treatment room.

If desired, the radium may at any time during the treatment be moved into the protected position by pressing another push-button. This stops the clock, which is restarted when the radium is moved down by pressing the first push-button. The clock will thus give the real treatment time irrespective of the number and durations of any interruptions.

The time required for moving the radium from the protected position to the nozzle or back is about 5 or 6 seconds instead of 20—25 seconds in the previous unit.

It will be seen from the illustration that the radium is spread over a ring-shaped surface, and that the nozzle embodies a cone. This cone, consisting of lead and tungsten, is intended to increase the relative depth-dose by decreasing the surface intensity without affecting the absolute depth-dose, as described in an earlier paper (5). If desired, the cone may easily be removed for the treatment of superficial lesions.

Two units of this type have been installed at the King Gustaf V Jubilee Clinics of Lund and Gothenburg, and two more are being made for Radiumhemmet. The reason why new units were installed at Lund and Gothenburg before Stockholm was that the previous units of the two former clinics were of older design entailing great irradiation risks to the staff, while Radiumhemmet had SIEVERT units with mechanical and pneumatic radium conveyors, as previously described, reducing the irradiation risks considerably.

SUMMARY

The paper describes an improved design of SIEVERT's teleradium apparatus, in which the radium is conveyed to and from a protecting lead container by means of a remote control mechanical device.

ZUSAMMENFASSUNG

Es wird eine verbesserte Ausführung von SIEVERT's Teleradiumapparat beschrieben, in der das Radium zwischen dem eigentlichen Bestrahlungsapparat und einem Schutzbehälter aus Blei mit Hilfe einer fernbedienten mechanischen Anordnung befördert wird.

RÉSUMÉ

L'auteur décrit une construction perfectionnée de l'appareil de télécuriethérapie d'après SIEVERT dans laquelle le radium est transféré entre l'appareil d'irradiation proprement dit et un cylindre protecteur en plomb, à l'aide d'une construction mécanique contrôlée à distance.

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THE DISTRIBUTION OF RADIATION IN THE TREATMENT OF CARCINOMA OF THE CERVIX[1]

by

Malcolm Donaldson, M.B., B.Ch., F.R.C.S., F.R.C.O.G.

I feel that it is indeed a privilege to be asked to contribute to this special edition of Acta Radiologica which is dedicated to Professor HEYMAN. There are others who are more capable than I am to describe the great influence that he has had on radiotherapy throughout the world, but I must record a common incident which »speaks volumes» concerning his influence in England. If during a simple qualifying examination in gynaecology the candidate is asked what radium technique he knows of or has seen for treatment of carcinoma of the cervix his answer invariably is »Heyman's». It is not often that he really knows anything about such treatment, but he uses this word »Heyman» as a talisman or »open Sesame» to get him through the examination.

Although cancer of the cervix has been treated by radium since 1903 (1) yet it is only in recent years that real consideration has been given to accurate measurements of the amount of radiation that is received by the various parts of the pelvic tissues. In the early days radium was used with very little screenage. In 1907 the question of filtration was first raised by DOMINICI (2), and after this it was realised that better results could be obtained by cutting out all but the gamma rays. The dose was empirical and expressed in such terms as »milligram hours» and E. S. D. and it was not until 1937 that the roentgen unit was finally defined for radium. In 1932 SIEVERT (3) measured the dose of radiation received in different parts of the rectum from the radium used in treatment of carcinoma of the cervix. Before this calculation had been made of the roentgen dose at various points in a »water phantom» and by other methods. Since then much work has been done on this subject. In 1935 QUIMBY and ARNESON (4) published a paper showing the distribution of radiation that occurred in various techniques then employed for treatment by roentgen rays of carcinoma of the cervix, the results being

[1] Submitted for publication, June 6, 1947.

given in % of an erythema dose, and another paper by LUCAS (5) describes the isodose curves of various radium techniques. In 1938 SANDLER (6) published a very important paper in which he points out how much the size of the vagina influences the dose of radiation far out in the parametria, and later in the same year TOD and MEREDITH published a paper (7). It will be seen later that NEARY has overcome this variation due to the size of the vagina by putting the Radium in the middle line. In 1941 MAYNEORD and HONEYBURNE (8) published a paper which primarily deals with the distribution of irradiation from containers used in the Marie Curie Hospital (1) in treating carcinoma of the cervix (2) in treatment of carcinoma of the body. It is of particular importance to note that the authors draw attention to the fact that the dose near the container may vary considerably with movement of the container in situ. It may be argued that experience has proved that such changes in position do not materially alter the result of treatment. That is difficult to disprove, but if progress is to be made it is essential that there should be a picture of the exact dose of radiation received by the tissues throughout the pelvis. All evidence so far suggests that the action of roentgen rays and radium is due to local changes and without such exact knowledge it will be very difficult to make any headway with the even more difficult problem of biological response. Much work has been, and is being done on this latter subject, both by animal experiments and tissue culture, and I think one of the big steps forwards is the work of SPEAR and GLUCKSMAN (9). These workers have shown that in the case of carcinoma of the cervix it is the well differentiated growth, and those that show the power to differentiate that are most likely to be affected by radiation and the patient cured. This is contrary to what was at one time believed, and it is true that *macroscopically* the undifferentiated quickly growing neoplasms often disappear rapidly, but microscopically the malignant cells are still present. These workers, moreover, have devised a method of cell counts by which the response of the tumour to the irradiation can be gauged within three weeks of treatment. This method is still being tried out, but the results to date suggest that it is a »True Bill». The value of this method is two fold: first because in early cases *i. e.* Stages I and II if the growth does not respond, hysterectomy can be carried out, and secondly it can be used to gauge the value of new techniques without waiting five years for the results. There is still much need for research into technique, investigation into the subject of intensity factor and time factor are by no means exhausted. For all such work an exact knowledge of the physical dose is essential. After reading these papers and as a result of my own experience it becomes obvious that some technique must be devised (1) for keeping the container fixed in relation to the pelvis, (2) to get a better distribution of irradiation

Fig. 1. Complete applicator assembled as unit.

Fig. 2. Applicator with external fixing apparatus.

Fig. 3. Applicator during construction, without nickel shell, to show form of platinum screens.

Fig. 1.

Fig. 2.

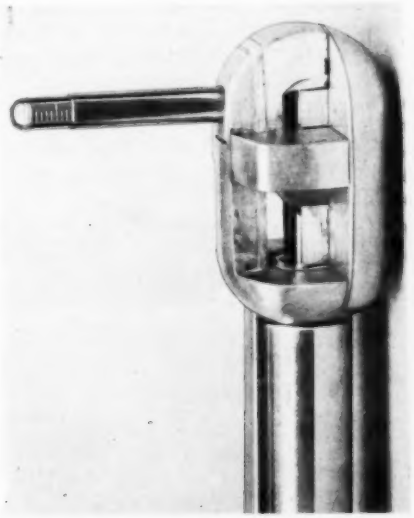

Fig. 3.

to the deeper parts of the pelvis, (3) to be certain of the dose given by the radium to certain points in the pelvis, so that in cases where roentgen rays are combined in treatment, there shall not be too large a dose where the radiations overlap.

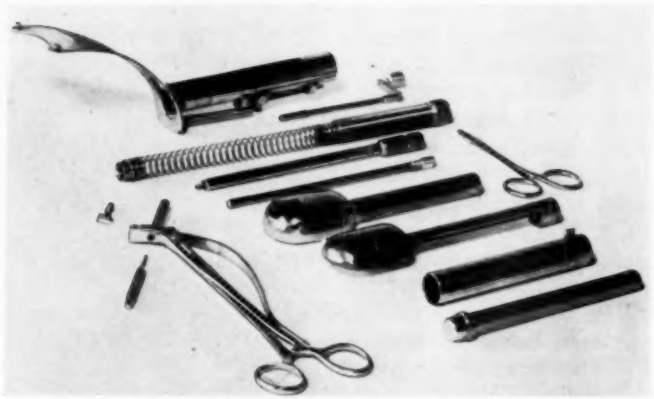

Fig. 4. Component parts of applicator.

Dr. NEARY (10) very kindly undertook this piece of research, which is published in two parts. In part I before discussing the physics of the problem he takes as the basis of his arguments the following statements:

(1) The disease is in a large proportion of cases confined to the true pelvis.

(2) The general spread of the disease is laterally into the parametria and lymph nodes; in a very appreciable proportion of cases even of the earliest cases, the parametria, or the lymph nodes, or both, are already involved.

(3) Intracavitary radium at present plays a fundamental part in the treatment of the disease. The improvement in results by combining supplementary roentgen treatment is generally admitted to be disappointingly small.

He sums up the ideals to be aimed at as (1) a certain fixed dose (the optimum non necrosing dose) at point A. Point A is taken as the ureteric canal in the parametrium *i. e.* two cms. from the middle line and 2 cms. above the vault of the vagina. (2) as great a dose as possible at point B 5 cms. from the middle line and on the same plane as A. (3) an upper limit to the dose at point S which is the rectovaginal septum opposite the cervix. The author then analyses the dose received at these points in various techniques, pointing out that the contribution of the uterine tube to the dose received at point B is poor, and that the radiation received from the vaginal applicator varies widely with the size of the vagina. This latter point was emphasised by SANDLER in his paper.

Part II is a detailed investigation of the dose received from a technique evolved by myself (a modification of the Heyman technique), namely

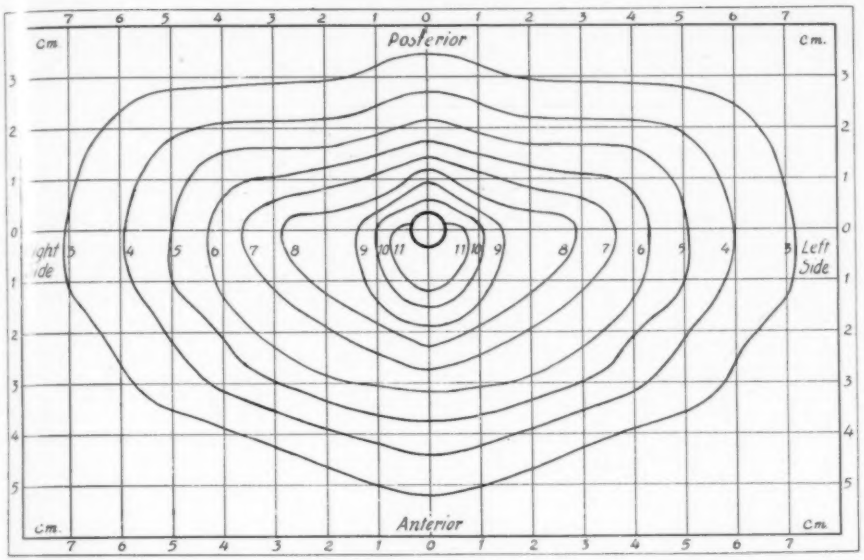

Fig. 5. Isodose curves in transverse plane (perpendicular uterine axis) 2.5 cm above external os; the numbers on the curves refer to doses in multiples of 1,000 r for a treatment time of 72 hours.

the tube and butterfly pessary. This technique also shows a poor dose at B, not more than 1,900 r in 72 hours.

In part I of his paper NEARY showed why theoretically it would be better to have the vaginal radium in the middle line, and now he has with the help of the author, designed an applicator which has the following advantages. (1) When in position the uterine and vaginal portions of the applicator are fixed together to form one unit. (2) treatment by this instrument gives in 72 hours a dose of radiation on the cervix at the external os of 10,000 r, at point A 8,000 r, and point B 5,000 r over an area of 3 × 2 centimetres. (3) the applicator is fixed by means of harness. (4) even if there were a slight movement, which is extremely unlikely, the radium in the vagina is so far from the nearest tissue as to make the change in dose very slight indeed. A full description of this applicator which has been used on 32 cases at Mount Vernon Hospital during the last twenty months is now in the press, and a brief description of it must suffice in the present article. The applicator originally consisted of a uterine tube containing 70 milligrams of radium, active length 7 mm. placed high up in the tube and has a platinum filter in the pos-

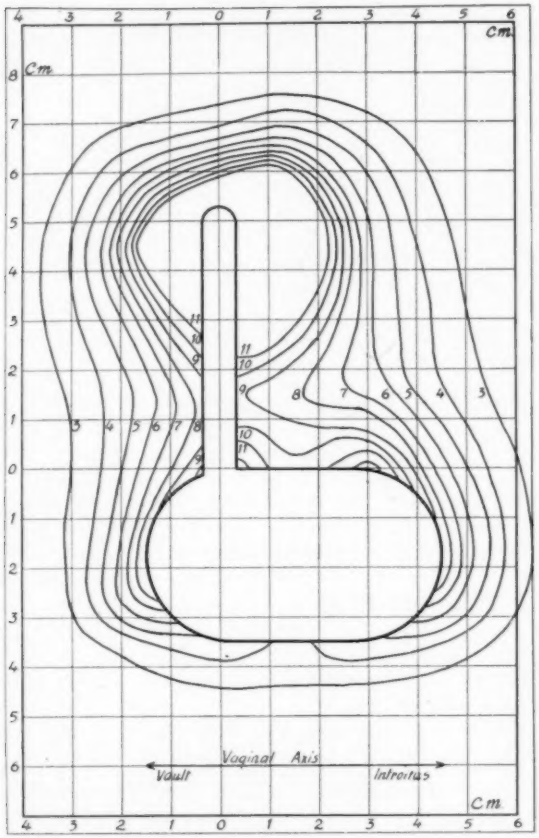

Fig. 6. Isodose curves in median sagittal plane; the numbers on the curves refer to doses in multiples of 1,000 r for a treatment time of 72 hours.

terior aspect of 3 mm. in thickness. This tube has attached to it a thin steel strip which, when threaded through the vaginal applicator, is used to anchor the uterine tube firmly to the vaginal applicator. The vaginal applicator is made in two parts, the anterior containing, when in situ, the radium, the posterior, made of platinum, acting as a spacer and screen to protect the rectum. The two halves are held together by means of a sleeve and after the harness is in position, finally the vaginal radium, 240 mgs in all, at the end of a long steel tube is placed inside the handle of the container, and screwed into position. The anterior half of the vaginal portion of the container is made of platinum with carefully designed windows to allow of the proper distribution of the radiation.

It was decided to give a continuous dose of 72 hours so as to be able to compare the cell counts with other cases which were treated by the »tube and pessary» for the same length of time. It is too early to draw any conclusions from the clinical results. Of the 32 cases 23 patients are alive, the longest period being only 20 months. It is certain, however, that the radium in the fundus of the uterus is too concentrated, giving rise in at least two cases to large necrotic abscesses and injury to the intestines from which the patients eventually succumbed. Dr. NEARY is now modifying this defect but, as already stated, the uterine radium

ontributes only a small amount to the pelvic wall, such modification ill make little difference to the general picture of isodose curves.

Dr. BLOMFIELD of Sheffield has also designed a vaginal applicator ith the radium in the middle line.

SUMMARY

The necessity for an exact knowledge of the distribution of radiation is essential to the further advances in the treatment of carcinoma of the cervix by means of radium. A brief description of a vaginal and uterine applicator is given, which produces isodose curves far more advantageous than those of any applicator so far made.

ZUSAMMENFASSUNG

Die genaue Kenntnis der Verteilung der Strahlung ist notwendig für weitere Fortschritte in der Behandlung des Zervixkrebses mit Radium. Es wird eine kurze Beschreibung eines Applikators für Scheide und Gebärmutter gegeben, der bedeutend vorteilhaftere isodosische Kurven gibt als alle bisher hergestellten Applikatoren.

RÉSUMÉ

La nécessité d'une connaissance exacte de la distribution de la radiation est la condition essentielle de nouveaux progrès dans le traitement du cancer du col par le radium. Déscription succincte d'un applicateur vaginal et utérin qui donne des courbes isodoses de beaucoup plus avantageuses que celles de tous les applicateurs construits jusqu'ici.

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FROM THE RADIUMHEMMET (CHIEF: PROF. E. BERVEN) AND THE RADIOPHYSICAL INSTITUTE (CHIEF: PROF. R. SIEVERT) OF KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM

SMALL-SCALE DOSAGE TRIALS FOR PREPARATORY STUDIES IN RADIOLOGICAL TREATMENT[1]

(Preliminary report)

by

Dr. *A. Nicolaeff* and *R. Thoraeus*, D. Sc.

Before the beginning of any radiological treatment series each patient is thoroughly examined. On the basis of the result the number, position and size of the fields and simultaneously also the respective directions of the beam are planned in detail. With due consideration and by calculation of the dosage conditions the complete treatment plan is then finally decided upon. Since, however, uncertain factors, for instance percentage depth dose, are included in the calculation, it would seem very desirable to get a reliable check of the calculations and a survey of the dosage efficiency of the treatment plan before this is put into effect. To meet this demand it was suggested by one of us (THORAEUS) about two years ago, to make dosage trials on the treatment plan, using but small amounts of radiation. This trial method may be applied as follows.

Small condenser chambers are placed singly, or suitably in pairs at the centres and, in cases of oblong fields, also at the ends of all the fields. In cases of a cavity being accessible, depth dose measurements may be carried out by applicating into the cavity a number of chambers, contained in a sound-tube of a suitable material. In this tube the chambers are placed one above the other from the closed end of the tube. All the chambers mentioned shall remain in their respective positions during the course of the trial, thus recording the total amount of radiation received.

Small amounts of radiation — corresponding to the sensitivity of the condenser chambers and suitably in proportion to the skin doses of the treatment plan — are now given to each field, one after the other, using the proper adjustment of the beam and the particular protection

[1] Submitted for publication, June 19, 1947.

round each field. Before each irradiation an additional pair of chambers is placed at the centre of the field which is to be irradiated, and remains there only during that particular irradiation. These additional chambers will thus only record the dose directly given to each field. The complete treatment plan being accomplished on a small dosage scale, the chambers are removed and read, and an average for each pair calculated.

The method of measuring described may be characterized as a preparatory study of the dosage efficiency of the complete treatment plan. Such a small-scale study of the treatment plan enables us immediately to get a survey of the skin dose and its distribution upon the fields used, of the resulting depth dose, and finally, of the distribution of depth dose along the centre-line of the chamber-containing part of the sound-tube. From the results of such a trial we may then easily calculate the dosage values corresponding to the full-scale treatment plan. The trial method can be used in all cases of radiological treatment series using a single field, or multiple field, or rotation technic. It may also be of value for the comparison of alternative treatment plans and of the dosage efficiency of beams of various penetrating power. It always yields skin dose values and in addition, depth dose values in cases in which a cavity is accessible for the application of a sound-tube in which condenser chambers are contained. The only means required is a sufficient number of small condenser chambers of a suitable measuring capacity, of a maximum of 100 to 150 r.

Since only small amounts of radiation are required for a dosage trial, this will not interfere with the treatment plan, and the doses recorded during the trial may always be exactly corrected for. In most cases such a trial may be accomplished by giving at most some 50—100 r to each field, *i. e.* on a dosage scale smaller than 1 : 10. The time required for a trial of a complete treatment plan will then be $^1/_2$—$1^1/_2$ hour. Even in cases where repeated trials have to be carried out, for instance because of required modifications of the treatment plan, or where alternative treatment plans are to be compared by trials, the doses applied during the repeated trials are still relatively small, and they may always be exactly corrected for in the treatment plan finally adopted.

The application of this method is, however, as far as depth dose measurements are concerned, closely connected with the problem of finding a suitable material for the sound-tube. In fact, the method was first suggested when a satisfactory solution of this problem had been found. After much searching one of us (THORAEUS) found a synthetic material or plastic, polyvinylchloride, which has proved to meet the requirements of this particular purpose very well. At temperatures of about 37° C a sound of this material is very soft and flexible, and thus

closely follows the contours of the cavity. Furthermore, such tubes have a very smooth surface, causing but little irritation when applied to cavity. One end of a sound-tube may be closed by careful heating over a gas burner, the closed end simultaneously being well-rounded by applying a mould to the tube. The external measurements of our cylindrical condenser chambers are 20 mm in length and 5 mm in diametre[1] Accordingly we use sound-tubes having an internal diametre of 6 mm., a wall-thickness of 0.7 mm and an external diametre of 8.4 mm. The polyvinylchloride is not dissolved or damaged by alcohol of high concentration, this fluid is therefore suitable for cleaning and disinfecting purposes. Tubes of this material may be had in various colours. For the purpose considered, the uncoloured and transparent quality is, however, to be preferred.

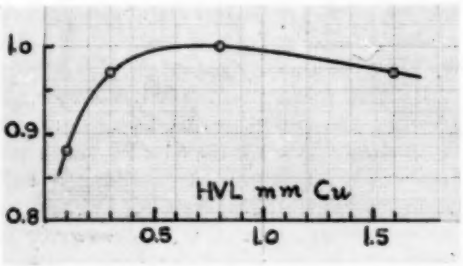

Fig. 1. Transmission of the sound-tubes.

In using polyvinylchloride as the material of the sound-tubes, it may be of interest to know how far the absorption in this material influences the records of the condenser chambers. To acquire the information required chambers were irradiated at 60 cm focal distance and free in air, some of them within a sound-tube, the others without sound-tube. Such comparative series were taken for four beams of half-value layers (HVL) between 0.1 and 1.6 mm of copper. The average results calculated are given in fig. 1., where the transmission, *i. e.* the ratios of the records obtained with and without sound-tube, is plotted against the HVL of the beam used. As may be expected, the results show that for HVL-values below 0.3 mm of copper an evident absorption occurs in the wall of the sound-tube. Since, however, only beams of HVL-values above 0.5 mm of copper are used in deep therapy, the absorption is without practical importance and we may assume that the dose records are correct within about two percent. The results included here refer to sound-tubes of red coloured polyvinylchloride, the uncoloured quality not being available at that time.

The method of increasing the depth dose by cross-fire irradiation on the basis of multiple fields is well-known and commonly used in radiotherapy. The application of this method is based upon the fact that the normal skin and the sound tissues have a maximum tolerance against radiation and that this tolerance should not, if possible, be exceeded

[1] R SIEVERT: Acta Radiol. Vol. XV, 1934, p. 197.

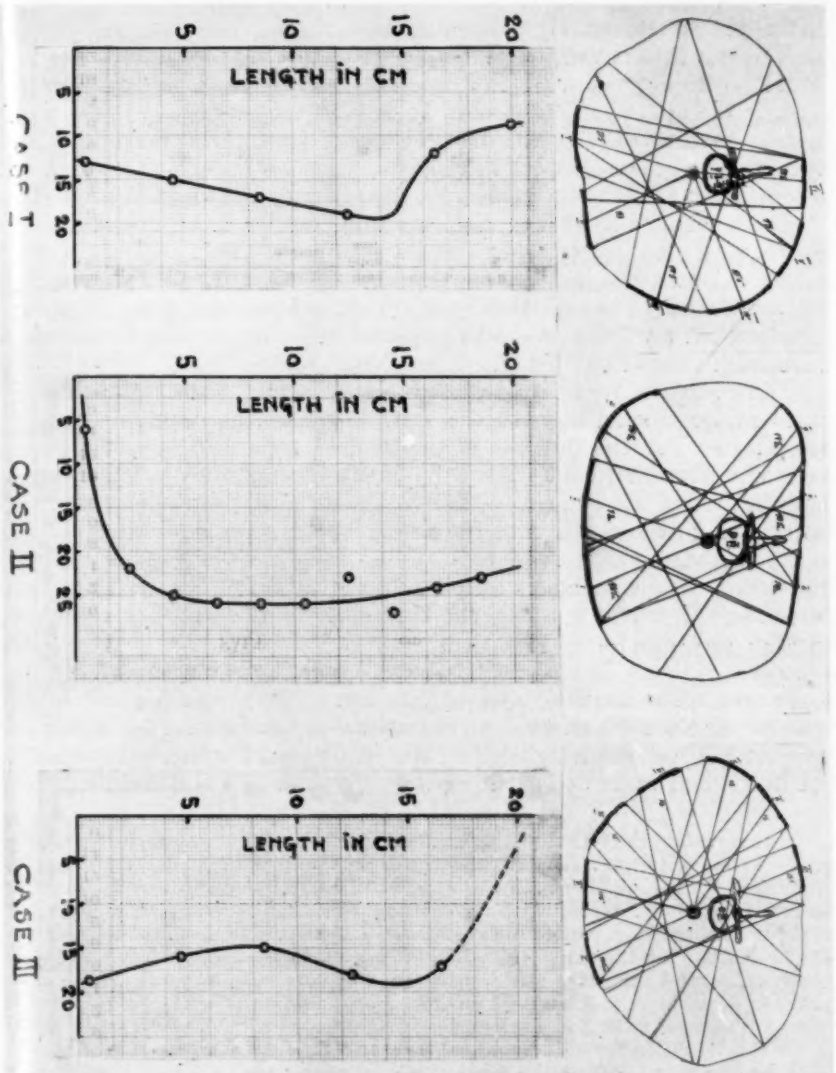

Fig. 2. Distribution of percentage depth dose along the centre-line of the sound-tube in the oesophagus. Zero of length-scale denotes the closed lower end of the sound-tube.

during the treatment. By using a number of fields and directing through each field a beam against one same part of the body volume it has been found possible to increase the dose received by that part without exceeding the tolerance of the skin. It is, however, not always possible by measurements to follow the distribution of dosage in a body irradiated by cross-fire beams. During the last years the authors have been able to accomplish some series of measurements referring to cross-fire irradiation.

In the following we communicate trial results in 3 patients in connexion with roentgen treatment at the Radiumhemmet. The examination of the patients, the detailed planning of the treatment series including the calculation of the depth dosage from the average depth of the oesophagus from all fields[1] and the application of the condenser chambers have been carried out by one of us (NICOLAEFF).

The dosage trials refer to cross-fire irradiation of the thorax and include measurements of both the skin dose and the depth dose in the oesophagus. For the purpose of depth dose measurements, the sound-tube was introduced into the oesophagus through the mouth, so that the position of the condenser-chamber containing part of the tube corresponded to the position of the fields. Fig. 2 gives individual sections of the thoraces, position and breadth of all the fields and the corresponding beams. Below each section we give a diagram of the distribution of percentage depth dose along the centreline of the chamber-containing part of the sound-tube (length of this part 20 cm, total length of the sound-tube about 45 cm). All the cases refer to a target-skin distance of 60 cm, an additional filter of 0.5 mm Cu + 1 mm Al, and a tube voltage of 169 kV constant and continuous potential. The half-value-layer of the radiation used is 0.8 mm of copper. Further particulars of the individual cases are given in the following.

Case I. Length of all the fields = 16 cm. Breadth of the fields = 6—8 cm. Average field area = 100 cm². The circumference of the thorax = 91 cm and the sum of the breadths of the fields = 44 cm. The average depth of the œsophagus as calculated from the section is 14 cm. According to the commonly used tables a percentage depth dose of 21 per cent may be expected. A skin dose of 75 r was directly given to each field, *i. e.* $6 \times 75 = 450$ r for the whole trial. The corresponding irradiation time was 6×1.5 minutes. The total amount of radiation, received by each field during the course of the trial, was found to vary between 82 and 87 r, corresponding to a total of 508 r and an average of 85 r per field. These values show that the total amount of radiation received by the skin of the fields (508 r) is about 13 per cent greater than the sum of the skin doses directly given (450 r). The depth doses recorded during the trial were found to vary between 53 and 98 r. Comparing all the depth dose values with the total skin dose (508 r), we get the percentage depth dose values and their distribution as plotted in the diagram. The dosage trial results of this diagram indicate a maximum percentage depth

[1] E. BERVEN: »Radiological treatment of Cancer oesophagi», Lecture read before the Nordisk förening för medicinsk radiologi, Oslo 1939.

dose of 19 per cent, and from the distribution within the middle half-length of the sound-tube an average of about 17 per cent may be estimated.

Case II. Length of all the fields = 17 cm. Breadth of the fields = 7—9 cm. Average field area = 125 cm². The circumference of the thorax = 97 cm and the sum of the breadth of the fields = 46 cm. The average depth of the œsophagus as calculated from the section = 12.5 cm. According to the commonly used tables a percentage depth dose of 27 per cent may be expected. A skin dose of 72.5 r was directly given to each field, *i. e.* 6 × 72.5 r = 435 r for the whole trial. The corresponding irradiation time was 6 × 1.5 minutes. The total amount of radiation, received by each field during the course of the trial, was found to vary between 87 and 97 r, corresponding to a total of 546 r and an average of 91 r per field. These values show that the total amount of radiation received by the skin of the fields (546 r) is about 26 per cent greater than the sum of the skin doses directly given (435 r). The depth doses recorded during the trial were found to vary between 118 and 147 r. Comparing all the depth dose values with the total skin dose (546 r), we get the percentage depth dose values and their distribution as plotted in the diagram. The dosage trial results of this diagram indicate a maximum percentage depth dose of 26 per cent, and from the distribution within the middle half-length of the sound-tube an average of about 25 per cent may be estimated.

Case III. Length of all the fields = 18 cm. Breadth of the fields = 6—7 cm. Average field area = 110 cm². The circumference of the thorax = 96 cm and the sum of the breadth of the fields = 42 cm. The average depth of the œsophagus as calculated from the section = 15 cm. According to the commonly used tables a percentage depth dose of 19 per cent may be expected. A skin dose of 95 r was directly given to each field, *i. e.* 7 × 95 = 665 r for the whole trial. The corresponding irradiation time was 7 × 2 minutes. The total amount of radiation, received by each field during the course of the trial, was found to vary between 105 and 130 r, corresponding to a total of 791 r and an average of 113 r per field. These values show that the total amount of radiation received by the skin of the fields (791 r) is about 19 per cent greater than the sum of the skin doses directly given (665 r). The depth doses recorded during the trial were found to vary between 126 and 139 r. Comparing all the depth dose values with the total skin dose (791 r), we get the percentage depth dose values and their distribution as plotted in the diagram. The dosage trial results in this diagram indicate a maximum percentage depth dose of 18—19 per cent, and from the distribution within the middle half-length of the sound-tube an average of about 16 per cent may be estimated.

Although the results reported here are not very extensive, they illustrate the applicability of the trial method. Much valuable information as to the dosage efficiency of radiological treatment may be obtained by this method and, what is more important, may be obtained *before* the treatment is started. In the following some general conclusions, drawn from the results, are given.

For all treatment plans of more than one field it will be particularly noted that besides the dose directly given to the fields, each field will indirectly receive additional doses during the irradiations of the other fields. As may be seen from the trial results, the sum of the total amounts of radiation thus received by the skin of the fields may be up to 25 per cent greater than the sum of the skin doses directly given.

Since this difference in certain cases may be still greater, due allowance for it must be made in the treatment plan. Quantitatively the difference mainly depends on the number and position of the fields used, and on the corresponding directions of the beam. As may be expected, the trial results show that the difference is not exactly the same for all the fields. Even if the variation is not very great, its mere existence may be considered a direct reason for calculating the resulting percentage depth dose as the ratio of the depth dose recorded and the sum of the total skin doses recorded.

In comparing the percentage depth dose values obtained by cross-fire irradiation through multiple fields with those of the standard tables, it must be remembered that the latter ones refer to irradiations of a single field. In cases of multiple fields, as mentioned above, each field indirectly receives additional dosage during the irradiation of the other fields. Due to these additional doses the percentage depth dose results of the multiple field technic, as they are calculated above, may in general be expected to be somewhat smaller than those of the single field technic, other conditions assumed to be constant. With due consideration to this fact, it would seem to be more adequate to use the term »percentage depth dose efficiency of the treatment plan» in connexion with multiple fields and rotation technic, and the term »percentage depth-dose» exclusively in connexion with the single field technic. By such a differentiation no confusion will occur.

Further investigations of radiological treatment series by means of trials are going on.

SUMMARY

As a method for preparatory dosage studies in radiological treatment, it is suggested to make dosage trials of the complete treatment plan, using but small amounts of radiation. Such a small-scale study or trial will give a survey of the dosage efficiency of the treatment plan before this is put into effect. By means of dosage trials some cases of cross-fire irradiation of the thorax have been investigated. From the result obtained some general conclusions pertaining to skin dose and percentage depth dose efficiency are drawn.

ZUSAMMENFASSUNG

Die Vornahme von Bestrahlungsversuchen mit kleinen Strahlendosen wird als eine Methode für vorbereitendes Studium der Effektivität radiologischer Behandlungspläne vorgeschlagen. Durch Durchführung eines Behandlungsplanes mit nur geringen Dosen lässt sich ein allgemeiner Überblick der Dosenverteilung erzielen, ehe der Behandlungsplan endgültig zur Ausführung gebracht wird. Mit Hilfe solcher Bestrahlungsversuche sind einige Fälle von Kreuzfeuerbestrahlung des Brustkorbes untersucht worden. Aus den Versuchsergebnissen liessen sich gewisse allgemeine Schlüsse ziehen.

RÉSUMÉ

A titre d'étude dosimétrique préliminaire en matière de radiothérapie il est suggéré de faire des dosages d'essai du plan complet de traitement en n'utilisant que de petites doses. Pareille étude donnera un aperçu de l'efficacité du plan de traitement avant qu'il soit mis en œuvre. Certains cas d'irradiation du thorax par feux croisés ont été étudiés par le moyen de ces essais dosimétriques. Des résultats obtenus on a tiré quelques conclusions générales touchant la valeur de la dose cutanée et celle du pourcentage de la dose profonde.

FROM THE RADIOPHYSICAL INSTITUTE OF KING GUSTAF V'S JUBILEE CLINIC, STOCKHOLM
(CHIEF: PROF. R. SIEVERT)

TWO AUTOMATIC METHODS FOR MEASURING CONDENSER CHAMBERS[1]

by

Rolf M. Sievert

In radiation measurements using the condenser chamber method, it is sometimes necessary to make rapid measurements of large series of chambers of the same type. For this purpose, a rationalization of the measuring methods is essential. At the Radiophysical Institute, Stockholm, the demand for such an increase in the rate of measurement has occurred in two cases. One concerned daily routine work, which had been in progress over a considerable period in order to control the irradiation dose in roentgen treatment by using condenser chambers on the skin or in the cavities of the body. The other case concerned measurements with a very large number of condenser chambers intended for a special investigation. Two entirely different devices have been constructed for these purposes — one semi-automatic, and the other entirely automatic. Both have proved themselves to fill the requirements fairly satisfactorily. A short description of these two devices will be given in this paper.

I. The Semi-Automatic Method

An investigation of the time required for routine measurements with condenser chambers at the Radiophysical Institute has shown the following approximate distribution of the working time per dosage measurement.

Observations on electrometer incl. notation (about 8 readings)	1.7 min.
Covering the chambers and preparation for application and measurement	2.4 »
Calculation	1.6 »
Various	1.1 »
	6.8 min.

[1] Submitted for publication, July 3, 1947.

Since, as a rule, only a relatively small number (0—20) ionization chambers are measured in succession, a complete change-over to automatic methods has not at present been considered justified. It has, however, proved desirable to simplify the work of the personnel by decreasing manual operations and calculations. In order to facilitate the work with the electrometers, the special contact apparatus shown in Figs. 1—2 has been developed. With the aid of a small electric motor (A), the contact pin in the electrometer is elevated towards the chamber's (B) inner electrode, and by means of a simple electromagnetic arrangement (C), the measuring electrode is either connected to the earth or to the charging source. The necessary change-over takes place by means of a mechanical contact. The different movements are controlled from a keyboard (D) by aid of a set of relays (E). By pressing the first button, the measuring electrode of the electrometer is earthed; by pressing the second, this electrode — as well as the chamber — is charged. The third button brings the measuring electrode into contact with the inner electrode of the chamber. The fourth button is used when it is not desired to read the charge remaining after irradiation but to find directly the loss of charge caused by the irradiation. This takes place by the application of a suitable voltage to the outer surface of the condenser chamber.

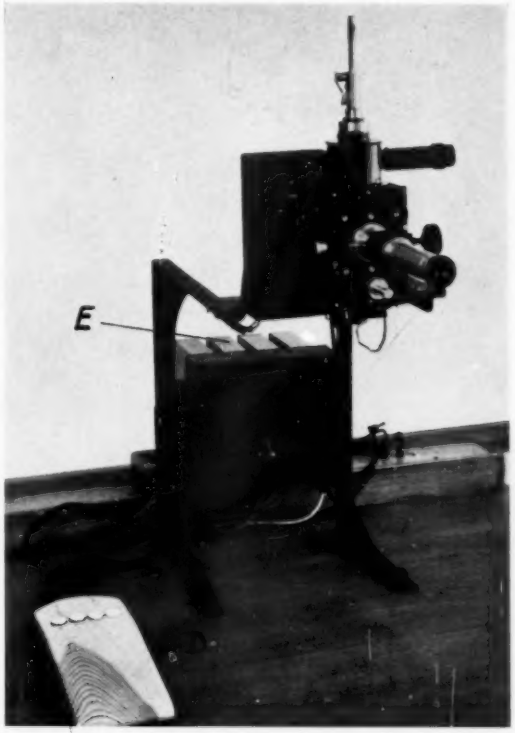

Fig. 1.

By means of the device described, considerable time is saved in making the readings, and the observer can comfortably take notes of the values obtained, at the same time as the readings are made. The device is used principally for condenser chambers for the measurement of

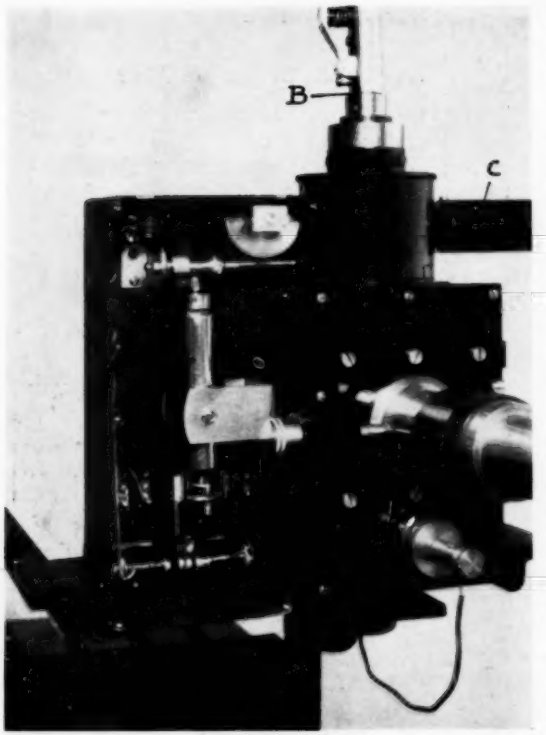

Fig. 2.

roentgen doses in the region of 50—500 r. The construction of the chambers has previously been described in this Journal.[1] The semi-automatic contact device was constructed at the Radiophysical Institute by Mr. AXEL BERGGREN under my direction. Now, after a year's trial, it has shown itself to function adequately.

For rapid calculation of the irradiation dose, an apparatus previously described in this Journal by BENNER is still in use.[2]

II. The Entirely Automatic Method

This device, which has been constructed mainly for relatively large and heavy condenser chambers of high sensitivity, is seen in Fig. 3. The instrument consists of a contact device (A) driven by an electric motor, a single string electrometer (B) and a photographic registering cassette (C) — the two latter, according to the Lutz-Edelmann design. The chambers are placed one after the other on the movable table (a), which is automatically raised and lowered by means of a motor (b). This motor also drives, through a shaft, the contact device (A), by means of which the electric contacts necessary for the earthing and charging and for changing the sensitivity of the electrometer are controlled. With the downward movement of the table, a spring for charging or earthing is brought into contact with the measuring electrode at (d). When the condenser chamber is placed on the table, a foot contact (e) is pressed. The motor starts, thereby lowering the chamber (a) towards

[1] SIEVERT, R.: Acta Radiologica, 15, p. 193, 1934.
[2] BENNER, S.: Acta Radiologica, 27, p. 243, 1946.

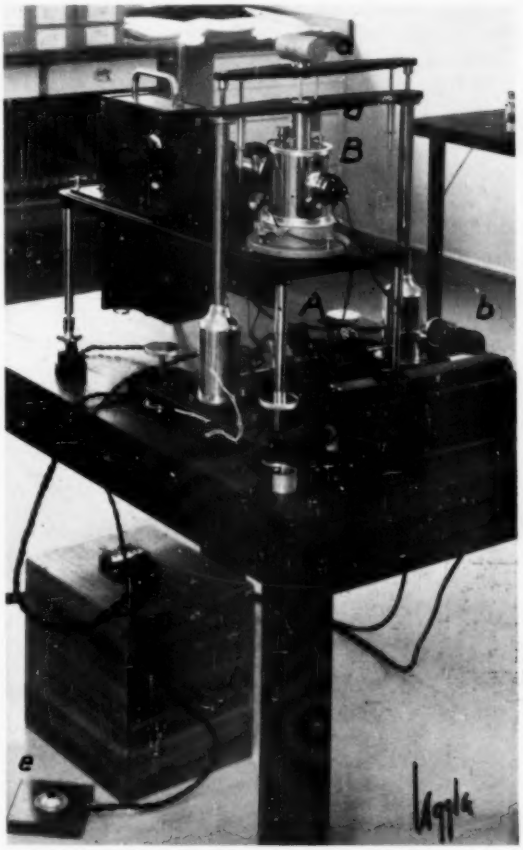

Fig. 3.

the electrometer. The charge of the chamber after irradiation is thus registered. The table then returns automatically to its original position and continues once more downwards, and a new contact between the inner electrode and the electrometer is established. Before, however, the table rises for the second time, the above-mentioned contact device switches the electrometer to lower sensitivity and charging takes place. The reduction of sensitivity is intended to avoid an excessive deflection of the electrometer string during charging. This deflection is registered. The table thereafter continues once more up and down, during which time the electrometer is again connected for full sensitivity. Thus the full charge value is registered at the subsequent contact between the electrometer and the chamber. In the next movement of the table, a switch-over to charging once more takes place so that the chamber is charged and ready for repeated use when the table returns to the raised position and the motor stops. In this initial position the original connections are restored in such a way that when the process is repeated with the next chamber, its charge after irradiation is registered as described above. The appearance of the registration is seen in Fig. 4. As the calibration curve of the electrometer is a straight line, it is easy to find the charge after irradiation as a percentage of the full charge by means of a special device seen in Fig. 5. A glass scale graduated from 0 to 100 is mounted on the object

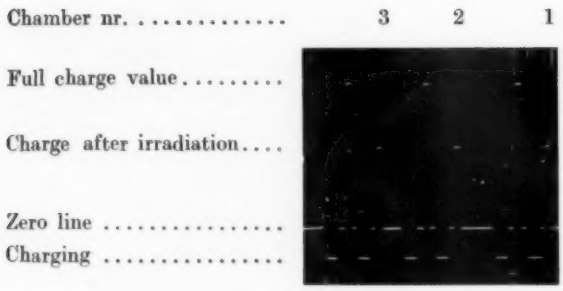

Fig. 4.

stage of a binocular microscope and the registration paper can be inserted under the scale. The sensitivity of the electrometer is adjusted so that the distance between the zero line and the deflection corresponding to the full charge is not larger than the distance between the lines 0 and 100 in the scale. By turning the scale and moving a rule, against which the registration paper is held, perpendicularly to the direction of registration, the line 0 of the scale can be made to coincide with the full charge deflection line on the paper and the line 100 on the scale with the zero line. When the paper is then moved along the rule, the lines which correspond to the charge after irradiation can thus be read off directly as a percentage of the full charge.

Fig. 5.

With the devices described, it is possible to achieve a measuring speed of at least 3—4 chambers per minute, including the reading of the registration curves. When making similar measurements without an automatic device, which in large series is extremely tiring for the observer, 1 chamber in two minutes is, as a rule, a maximum.

Automatic devices making it possible to use the condenser chamber method for very large measuring series can be of considerable significance, not least when it is a question of radiation investigations to assess the risks to which the personnel is exposed when engaged in roentgen work, or work with radioactive substances. In such cases, the necessity of accuracy in the readings is limited, and this renders the construction of automatic registration devices easier. In this connection, the most suitable method is probably that of electrometer valves combined with amplifiers and curve drawing recorders. It should be possible, without any great difficulty, to achieve an entirely automatic measurement of 5—10 chambers per minute. Considering the increase of radiation risks which must accompany advances in the field of atomic research, further development of the measurement method when using condenser chambers appears to be of importance. In cases where radiation measurements would be required on a very large scale, the condenser chamber method, on account of the very low cost per measuring instrument, could be expected to prove suitable for the purpose. The fact that the person bearing the chamber during the work is unable himself to make radiation observations is, from a psychological point of view, an advantage in many cases, and is a further argument in favour of this method.

SUMMARY

The author describes two methods, one semi-automatic and one entirely automatic, for measuring condenser chambers. These methods have been used for some time at the Radiophysical Institute in Stockholm.

ZUSAMMENFASSUNG

Der Verfasser beschreibt zwei Methoden, eine halbautomatische und eine vollautomatische, für Messung von Kondensatorkammern. Diese Methoden werden seit einiger Zeit am Radiophysikalischen Institut in Stockholm angewendet.

RÉSUMÉ

L'auteur décrit deux méthodes, l'une sémi-automatique et l'autre entièrement automatique, pour la lecture des chambres condensateurs. Ces méthodes sont en usage depuis quelque temps à l'Institut de Radiophysique à Stockholm.

FROM THE OBSTETRICAL AND GYNAECOLOGICAL CLINIC, DEPT. I, UNIVERSITY OF HELSINKI, FINLAND (CHIEF: PROFESSOR M. RAURAMO)

A DOSIMETER FOR PREVENTING RADIATION INJURIES TO THE RECTUM DURING TREATMENT OF CARCINOMA OF THE UTERUS WITH RADIUM[1]

by

Harry Zilliacus

The aim of radiation treatment of carcinoma of the uterus is to obtain the greatest possible destruction of the tumour. At the same time surrounding organs must be saved from radiation injuries. The radiation doses used to-day are not sufficient to cure all cases of carcinoma of the uterus, but the risk of causing damage to adjoining organs has hitherto limited the size of the radiation doses. The roentgen radiation given in conjunction with the radium treatment may contribute towards manifesting latent radium injuries in the pelvic organs, but it is the treatment with radium applied in vagina and uterus that causes most of the radiation injuries and more especially those in the rectum.

Despite much experience in this field certain risks are still taken in treating carcinoma of the uterus with radium. Quite apart from the technique used in the application of the radium (Stockholm, Manchester, Paris technique, implantation of radium needles) it is impossible to be absolutely sure that the radium has been applied in an ideal position. Different positions of the uterus, variations in the thickness of the recto-vaginal or vesico-vaginal septum, possible adhesions between the pelvic organs, and above all incorrect application of the radium, may all contribute towards causing the radium to lie in a position not absolutely ideal in every case. Moving the patient after the application, uncontrollable movements made by the patient when waking up after the anaesthetic, and the movements of the patient while the radium is in position, may all have an effect on the position of the radium. As a

[1] Submitted for publication, June 2, 1947.

consequence of this, the radiation which is lost to the tumour goes instead to adjoining organs. The result may be disastrous for the patient, in more than one sense of the word.

The frequency of late manifest rectal injuries was very high in earlier years. Now it is 5 to 10 per cent. In 1927 HEYMAN reported a figure of 10 per cent, of cases with rectal injuries among 502 patients treated with radium, DÖDERLEIN observed, in 1930, 4.9 per cent of recto-vaginal fistulas among 870 cases of carcinoma of the cervix uteri treated with radium, and VON MIKULICZ-RADECKI, in 1935, found rectal injuries in 12.8 per cent, and fistulas in 4 per cent. TODD, CORSCADEN, KASABACH and LENZ (1938) held a similar view on the frequency of rectal complications after treatment of carcinoma of the uterus with radium.

According to current literature the smallest radium dose that still causes manifest rectal injuries is about 3,000 to 4,000 mg. el. hrs. HEYMAN observed in 1925 serious rectum damage only in cases that had received a vaginal dose of more than 4,500 mg. el. hrs., given in three separate treatments. In 1930, after two treatments had been given, the corresponding dose was 4,000 mg. el. hrs. According to INGELMAN-SUNDBERG (1947), who bases his views on an investigation on the intensity of radium radiation in the rectum with SIEVERT's condenser chambers (SIEVERT 1932), the maximum dose that will cause a manifest reaction in the rectum, by using the *Stockholm method*, is about 3,300 r units.

INGELMAN-SUNDBERG demonstrated in 1947 that the 5-year cure rate was higher in patients with rectal injuries than in other cases. Among 3,392 cases of carcinoma of the cervix uteri treated with radium (at Radiumhemmet, Stockholm, 1914—1937), the 313 patients with rectal injuries that were encountered showed about 25 per cent more of 5-year cure than in the other cases, as may be seen from figure 1. Even though, as the author points out, some of the most serious cases die before developing signs of rectal injury, and thus cannot be included in the statistical figures, this observation is an indication of the fact that the higher dosage per volume unit of tumour was advantageous for the cure rate.

There are very few reports in the literature on attempts to secure an effective control of the application of the radium in the vagina and the uterus, and to keep a check on the intensity of the radiation in the rectum. SIEVERT described, in 1932, condenser chambers for the registration of the intensity of gamma radiation in the rectum, by the *Stockholm method*. He placed a number (10—15) of the electrically charged ionization chambers in a flexible tube, which was inserted into the rectum after the radium had been applied. After 4—5 minutes the chambers were withdrawn from the tube. Measurements were made 2—3

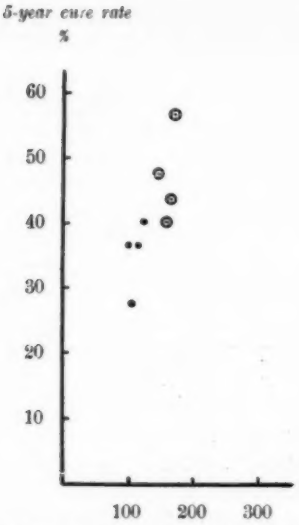

Fig. 1. The relation between 5 year cure and radium dosage (in mg. el. hrs. per cc. of tumour volume) in 626 cases of carcinoma of the cervix uteri treated at Radiumhemmet, Stockholm, during the years 1914 to 1937. Each dot represents a group comprising at least 39 and at the most 160 cases. The groups marked ⊙ denote cases with a rectal reaction (INGELMAN-SUNDBERG, Fig. 19 Suppl. LXIV, Acta radiol. 1947).

times during the treatment. The loss of charge in each chamber was then determined with the aid of an electroscope. The loss of charge occurring in a chamber when the gamma rays pass through it and ionize the gas is proportional to the intensity of the gamma radiation. By determining the loss of charge in all the chambers which had been in the tube it was possible to determine the intensity of the gamma radiation in the different parts of the rectum. When radium was applied only in the uterus the intensity of radiation never, as a rule, exceeded 2—3 Imc. When it was applied in the vagina alone, a definite maximum for the gamma radiation was registered at a distance of 5 to 10 cm. from the anus, and in the case of combined intravaginal and intra-uterine application peaks amounting to 7—10 Imc. were registered. Physically, 1 Imc. is about 8.3 r/hr.

In 1942, CHYDENIUS recommended control of the position of the radium by roentgenography.

The most adequate method for the avoidance of radiation injuries in the rectum and simultaneous control of hte position of the applied radium is an instrument which directly furnishes information as to the intensity of the gamma radiation in the rectum. An apparatus of this kind has already been devised,[1] and preliminary attempts to use it for controlling the radiation intensity in the rectum when the radium has been applied in both vagina and uterus have shown favourable results.

The catheter used for the examination of the rectum during and after the application of the radium contains an ionization chamber sensitive to gamma radiation. The part sensitive to gamma radiation is confined to an area of one cubic centimeter in the tip of the catheter.

[1] The dosage meter has been constructed at the Department of Physics of the University of Helsingfors under the guidance of Professor LENNART SIMONS, who has also supplied the description of the apparatus.

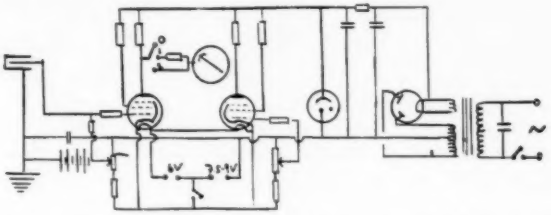

Fig. 2. Intensity meter for the measuring of the intensity of the gamma radiation in the rectum during application of radium in vagina and uterus. Wiring diagram.

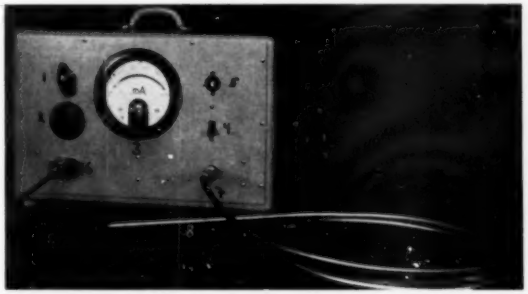

Fig. 3. Intensity meter for the measuring of the intensity of the gamma radiation in the rectum during application of radium in vagina and uterus.

1. Sensitivity switch, with three different positions, 0, 1, and 2.
2. Potentiometer for the zero point.
3. Milliammeter with a maximum of 100 milliamperes on the scale.
4. Switch.
5. Lamp that lights when the apparatus is functioning.
6. Cord for connecting up with the alternating current net.
7. Co-axial cord for the ionization chamber.
8. Casing for the ionization chamber (catheter), graduated in centimeters.

The ionization chamber, which is cylindrical, 15 millimeters long, and 10 millimeters in diameter, is mounted in a brass casing which forms one of the electrodes. The other electrode is a point in the axis of the cylinder. A 100 volt dry cell battery builds the electric field in the ionization chamber. In series with the dry cell battery and the ionization chamber is placed a resistance of 10^8 ohm. The potential across this resistance is measured with a vacuum tube amplifier consisting of two vacuum tubes of the El 6 type which are conducted in balance. The difference in the strength of the current in the anodes of the two vacuum tubes is measured with a 100 milliammeter. In order to obtain the best possible zero point constancy the detecting vacuum tube for the anode potential is stabilized

by a neon light. The heating current is taken from a 6 volt accumulator and the grid potential is delivered by a 9 volt dry cell battery.

Figure 2 shows the circuit of the dosage meter, and figure 3 the external appearance of the apparatus.

The sensitivity of the apparatus is such that 80 mg. of radium element, placed 1 centimeter away from the chamber, registers a tracing over the whole scale of the milliammeter. In the second position of sensitivity the tracing is one-fifth of the latter.

The following principles should be borne in mind when the dosage meter is used.

1. By calibrating the meter and dividing the scale into Imc or r per minute an area on the amplifier can be designated as a »danger zone» when using the ordinary treatment time. The total borderline dose is about 400 Imc hours (3,300 r) before a rectal reaction occurs, using the *Stockholm method*, which consists in two equal treatments with an interval of three weeks between them.

2. When radium is applied the rectum is examined with the catheter of the apparatus, and the least possible tracing on the meter (= the lowest gamma radiation in the rectum) should be aimed at. In any case, if the tracing extends into the »danger zone» the treatment should be shortened or a new application be made. Owing to the fact that only the point of the catheter is sensitive, the maximum (maxima) is readily found by taking recordings in various parts of the rectum. When the radium has been applied and the gauze packing has been applied in the vagina in such a way that as little radiation as possible penetrates to the rectum, the tracing (or tracings) on the ammeter and the distance between the anus and the tip of the catheter are noted. Attempts to apply the radium in such a position that the rectum will be as little affected by the radiation as possible should not result in the urinary bladder, the urethra, and the ureters being exposed to an overdose of rays.

3. By repeated control measurements, which require only a few minutes (after the anaesthetic, after moving the patient, and so on), it is possible to check up whether the radium is in the right position or not. If the meter registers a tracing into the »danger zone» a new application is indicated.

4. If the position of the uterus, adhesions, or other such factors cause the meter to register in the »danger zone» even when the application appears to be ideal, a reduction of the treatment time should be considered, and the possibility of complications due to overdosage should be pointed out to the patient.

5. If the meter shows very small tracings and the margin of the »danger zone» is relatively large a larger dose may be considered, always remembering, of course, that other organs may, in consequence of the increase, be subjected to an overdose.

SUMMARY

An apparatus is described which directly measures the intensity of gamma radiation i the rectum during gynaecological radium treatment. The instrument consists of a r bber catheter, in the tip of which an ionization chamber is situated in which a 100 v lt battery builds the electric field. In series with the battery and the chamber is placed a resistance of 10^8 ohm. The potential across this resistance is measured using a special a plifier.

ZUSAMMENFASSUNG

Es wird ein Apparat beschrieben, der die Intensität der Gammastrahlung im Rektum bei gynäkologischer Radiumbehandlung direkt misst. Das Instrument besteht aus einem Gummikatheter, in dessen Spitze eine Ionisationskammer eingebaut ist, in der ein 100-Volt-Element das elektrische Feld hervorruft. In Reiheschaltung mit dem Element und der Kammer ist ein Widerstand von 10^8 Ohm angebracht. Das Potential an diesem Widerstand wird mit Hilfe eines besonderen Verstärkers gemessen.

RÉSUMÉ

Description d'un appareil qui mesure directement l'intensité de l'irradiation par les rayons gamma dans le rectum pendant les traitements gynécologiques par le radium. L'instrument est constitué par une sonde de caoutchouc au bout de laquelle se trouve une chambre d'ionisation dans laquelle une batterie de 100 volts crée le champ électrique. Une résistance de 10^8 ohms est placée en série avec la batterie et la chambre. Le potentiel au travers de cette résistance est mesuré par un amplificateur spécial.

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FROM THE SURGICAL CLINIC OF THE SERAFIMER HOSPITAL, STOCKHOLM, SWEDEN
(CHIEF: PROFESSOR GUSTAF SÖDERLUND)

ON THE IMPORTANCE OF ROENTGEN DIAGNOSTICS ESPECIALLY IN THE SURGICAL CLINIC[1]

by

Gustaf Söderlund

HANS HELLMER in his recent inaugural lecture in the professorship of roentgen diagnostics at the University of Lund (Med. Fören:s tidskrift 1947, b. 2) gave an excellent description of roentgen diagnostics as a medical field of study. It may therefore seem presumptuous of a surgeon to enter upon the same theme. That this nevertheless is the case is due to the fact that the author during a collaboration of twenty-five years standing with two such outstanding roentgen diagnosticians as Professor ÅKERLUND and Professor LYSHOLM has had abundant occasion to appreciate the enormous importance of roentgen diagnostics — when at their best — in surgery; and it is also to some extent due to the fact that he is an independent roentgenologist for more than two years — in the childhood of roentgenology, it is true — has had occasion to experience and evaluate the tasks set before the roentgenologist, not only from the point of view of the consulting surgeon but also from the approach of the roentgenologist.

The importance of roentgen examinations in the diagnosis and indications within the entire field of clinical medicine, but perhaps mainly in the judgment of the surgical diseases, has not only in regards to diagnosis, but also from the point of view of treatment developed at a breathless pace within the last thirty or forty years. Methods of examination throwing bright light on anatomical details and functions in a succession of important organs, the roentgenology of which earlier was not even dreamt of, have at an increasingly rapid rate and with increasing perfection been placed at the disposal of the clinics.

During the first years following the discovery of the roentgen rays roentgen diagnoses were mainly of importance in direct photography of above all the roentgen-opaque tissues of the body, thus especially the skeletal system, and in the establishment of foreign bodies visible

[1] Submitted for publication July 1, 1947.

on the roentgen plate. A gigantic progress was made when the roentgenologic study of diverse of the hollow organs of the body was made feasible by filling these with a suitable contrast medium. The bladder was the first to be investigated in this manner; then followed suit, during the first decade of the century, the alimentary canal, especially the stomach, soon followed by the bowels and the renal pelvis. In 1911 HAUDEK and CLAIRMONT emphasized the great diagnostic importance of the niche symptom especially in ulcus disease, voicing at this early date the then extremely audacious theory that no previously known method of clinical examination gave as reliable an expression of the pathologico-anatomical changes, especially of the stomach, as roentgen. It would carry us too far to enter upon the roentgenology of the digestive canal. Suffice it to point out that the technic of examination which now is employed in all accurate investigations of mainly the surgical diseases of the stomach and the bowels to a very great extent is linked to FORSSELL's classical roentgen studies of the anatomy and physiology of the mucosa — studies, unfortunately not always duly appreciated in this country.

The surgeon KEHR, especially renowned for his work on the surgery of the biliary ducts, in the early 'twenties stated that it hardly was to be imagined that roentgen examination ever would become of material importance in the diagnosis of biliary calculus diseases. Only a few years were to pass before this opinion was clearly overthrown by the brilliant discovery of GRAHAM and COLE of *cholecystography* which for the first time in the history of roentgenology allowed an internal organ to appear on the roentgenogram by a contrast medium, not introduced into the organ itself but into the blood, and, later, following the intake of specific foods. Through this procedure not only the visualization of a concretion was made possible but cholecystography also permitted the diagnosis of diverse other morbid conditions of the biliary ducts; and through this method also the emptying mechanism of the gallbladder was studied in many cases.

Since thus through the discovery of GRAHAM and COLE this new form of roentgen diagnosis speedily was developed and made practicable, it was not long before urography, so eagerly awaited by the urologists, entered the scene. Already in the beginning of the thirties the first roentgenograms of a renal pelvis filled with contrast urine due to intravenous injection, *i. e.* urograms, were demonstrated. The introduction of urography may be considered to be revolutionary in the field of urologic surgery; through it a judgment of the normal and pathological anatomy of the kidney was rendered more exact than hitherto had been possible; the clinic also received a simple and valuable renal function test. Modern urography in addition gives an extremely valuable contribution to the

diagnosis of the acute abdominal cases as we by this method in an acute condition of pain have a means of determining with exactitude whether it is due to a ureterolithiasis or not.

To this brief survey of some of the most important milestones on the road of modern roentgen diagnosis towards its present high level shall only be added that in regards to the *lungs* roentgen examination now is considered indispensible and of greater value than any other method; that roentgen examination of the *heart* is an important detail in modern cardiology, and that to-day's advances in neurosurgery are very intimately associated with roentgenology. The important development of the last decades in regard to the treatment of especially the diseases of the *brain* and of the *spinal* cord would be inconceivable without the support of roentgenology. The outstanding contributions by the creator of neurosurgery in our country, OLIVECRONA, especially in the operative treatment of brain tumors are of course not entirely, but to a much further extent than the outsider realizes, made possible by the brilliant discoveries within the roentgenology of the brain by his collaborator LYSHOLM.

On thus reviewing this the rapid development of roentgenology to an indispensible diagnostic daily utilized in the clinics to an enormous extent, it lies close at hand to raise the following questions. Has the employment of roentgen examinations as a diagnostic measure now reached its climax in our clinics? Or is it reasonable to envisualize a further development, eventually on the discovery of new roentgen diagnostic methods of the same or similar magnitude as those mentioned above? Or is it possible to consider that roentgen examination with the diagnostic opportunities it already *at present* offers nevertheless is not so fully utilized as its great merits would justify, and that we accordingly for this reason should expect an increased frequency with demands on an increased capacity in our roentgen departments?

I for my part am firmly convinced that the peak on that curve which would indicate the needs of roentgen examinations of the surgical clinic has not even approximately been reached.

It seems highly plausible that the potentialities of Roentgen diagnostics are by no means exhausted, and that new methods will in the future be created, affording increased possibilities of penetration of the anatomy, the pathology and perhaps also the physiology of the human body. The previous course of the development of roentgen diagnostics points towards this decidedly. To this is also added the fact that according to the opinion of many surgeons the work in our clinics during recent years has made more and more demands on roentgen diagnostics to such an extent that roentgen has tended to become a *routine method of examination*. This trend may as yet only be clearly perceptible in certain hospitals and

in certain physicians in this country not infrequently in a fairly modest scale — this latter, however, probably due to the fact that the capacity of our roentgen departments neither in regards to space, apparatus nor staff are capable of coping with the clinic's constantly increased requirements of roentgen examinations. The curve of development, however, is clearly discernible, and shows that roentgen examination in a close future will be utilized on an enormously augmented scale. The time has passed when our clinics and hospitals only made a roentgenological examination of those organs which showed clinical signs of morbid changes and where the roentgen examination was exclusively or mainly done to *support* the clinical diagnosis. In many instances where the clinical diagnosis, as in a typical attack of biliary calculus, was considered definite, a roentgen examination was earlier considered superfluous or immaterial.

Since roentgen examinations of especially the abdominal organs and the kidneys and, to a certain extent, also the lungs, have been developed to such a degree that a negative result of the examination (*i. e.* no pathological changes being observed on the roentgen pictures) is considered nearly synonymous with the fact that the organ is healthy, roentgen examination naturally has been taken into play in order to *exclude pathological conditions* in certain organs. And since in many cases examinations done with such a purpose have roentgenologically established either pathologico-anatomical changes so early, so in the making, that clinical symptoms have not as yet arisen — in yet other cases revealing that considerable pathologico-anatomical changes are present *without clinical symptoms*, this has more and more established the enormous importance of roentgen as an early diagnosticum, or as affording a definite diagnosis in cases where the clinical symptoms have failed. The relative value of the clinical diagnosis has thus been revealed; it is many years since a surgeon, to take an example, was satisfied with considering the diagnosis in an attack of biliary calculus, be it ever so typical, so certain, that he considers operation without roentgen examination justifiable — hardly even in the case of a cholecystitits. A tender resistance in the region of the gall-bladder with other symptoms resembling an inflammatory process in this may be an infected hydronephrosis or — what has also been observed in our clinic — a cancer of the transverse colon.

The following case, observed more than ten years ago in our clinic, led already at that time to the re-organization of the preoperative routine examination in attacks of biliary calculus. The case was that of a female patient who was admitted for attacks of pain in the upper abdomen, suggesting cholelithiasis. The diagnosis was supported by cholecystography. At operation a gallbladder with thin walls without signs of inflammation was observed, a narrow, normal bile-duct, and in the gall-

bladder clear bile and about 10 stones, each the size of a hazel-nut. As this picture did not seem to explain the *pain*, duodenum was then examined; hereby was seen an ulcer the size of an egg in bulbus duodeni with edema of the surroundings and a markedly injected serosa; this was clearly the source of the pain.

In this clinic roentgen examination of the stomach *also* always is done in cholelithiasis and in quite a few cases — similar to that described above — the coincident presence of both gallstone and stomach ulcer have been observed, hereby enabling the surgeon before the operation to decide or to take a standpoint as to whether cholecystectomy or stomach resection or possibly both, are indicated. It is true that the combination of gallstones and duodenal ulcers is relatively rare. There are on the other hand many cases in our records where the patient has sought advice for dyspeptic symptoms, eventually with pain suggesting stomach trouble, where the gastric juice examination has shown diminished hydrochloric acid values, where the roentgenogram has been negative, and the patient has received according medication. Since the roentgen examination has been extended to the gallbladder cholelithiasis, eventually in association with cholecystitis, has been established, and operation has led to improvement or health.

It may now be considered indisputable that the *gallbladder* and *stomach-duodenum* are so closely related, and that diseases in both of these organs give rise to such parallel symptoms, that a roentgen examination of but one of these organs is incomplete and may be misleading if the other organ also is not examined roentgenologically.

We have, however, as was mentioned above, more and more come to the conviction that on symptoms from the abdominal cavity, especially pain, roentgen examination *also* of the *kidneys* and *colon* ought to be carried out. As was stated above, an infected hydronephrosis may give a clinical picture extremely like a cholecystitis. But there are also other cases in which an omission to perform a roentgen examination of the kidneys, a urography, may lead to a mistaken diagnosis and an erroneous therapy.

Some years ago an internist, a stomach specialist, referred to me for operation a girl of 12, who had had severe attacks of pain in the region of the umbilicus. The diagnosis was rare in a child, namely a cyst of the pancreas, but was considered as established through roentgen examination of the stomach, which showed a constant filling defect in the roentgen picture of the stomach. Operation showed no abnormality of pancreas and the pains continued. Some months later it was due to urography established that she had an intermittent hydronephrosis on the left side, and that the dilated renal pelvis was the cause of the filling defect and the pain. On ligation of an accessory vessel she became well.

As still another example of the importance of urography will be c ted the case of a woman, 20 years old, who was admitted to this clinic f r rather undefined »stomach-ache». Kidney, stomach and colon were r entgen examined with negative result; on consulation with the Medical (mnastics Department the diagnosis of ischio-lumbago was made and s e was treated for this condition for a couple of months. Some years l er she returned with increased complaints; urography revealed a horse- s oe kidney with hydronephrosis; after operation she became free of s mptoms.

In both of these cases the urine was normal and there was no evidence o renal infection. In the great majority of those cases in which the urine is macroscopically bloody urography is clearly indicated for the surgeon. The tendency within internal medicine has generally the same trend, although not quite so markedly. In this connection I wish to cite two cases, which were treated for hematuria at a medical hospital department, the one a man who had been hospitalized at various periods, for about 2 years, the other a young woman who had been treated with bed rest and diet for 6 weeks.

When the first case at last was examined urologically the cause of the hematuria was established, namely: a tumor of the bladder with a narrow pedicle and a benign appearance. Histological diagnosis: *Cancer*. Roentgen and radium therapy notwithstanding there was recurrence which later necessitated extirpation of the bladder according to Coffey. It is not impossible that urography, done at the time of the first establishment of the hematuria might have led to such an early treatment that removal of the tumor would have sufficed.

In the case of the young woman, roentgen examined after the lapse of 6 weeks, a filbert sized calculus in one of her kidneys was shown to be the cause of the hematuria.

In both of these cases the patients had been treated under the diagnosis of chronic glomerulonephritis. According to the testimony of internist authorities a hematuria without roentgen examination of the urinary apparatus may — as in the two cases cited above — be interpreted as a chronic glomerulonephritis, when actually a condition was present which required surgical therapy. Even though perhaps the great majority of cases of hemorrhagic glomerulonephritis may be diagnosed without ro ntgen examination, there nevertheless are hematurias where the ab olute exclusion of the presence of a surgical hematuria is so difficult or so uncertain that urography is clearly indicated.

It is evident that in the *complete* roentgen examination of the abdomin l organs and kidneys, which has become increasingly more common in our clinic, the various organs are to be examined in a definite sequence. E en although the symptoms may suggest a stomach lesion the stomach

ought as a rule not to be examined first, as the contrast introduced into the alimentary canal for days or even for weeks may render examination of the kidneys and biliary system out of the question. The order of precedence ought to be 1) gallbladder and kidneys, 2) colon, *i. e.* contrast enema, which is fairly easy to wash out, and 3) finally the stomach, eventually in combination with a so-called motor test meal examination of the entire bowel canal.

In this connection the author would like to touch upon the routine roentgen examination also of the *heart* and more especially of the *lungs* in surgical praxis. It seems quite evident that routine roentgen examinations of the heart, especially in young patients about to be subjected to a minor abdominal intervention, such as an appendectomy, is unessential. The lungs are more important. It is generally recognized that particularly in children a small pneumonia, medially or diaphragmatically situated, may give arisal to symptoms deceptively similar to those of appendicitis. It has also been observed that particularly low and deeply situated pneumonias also in adults may give abdominal symptoms, with board-like resistance in the epigastrium, thus strongly suggesting perforating ulcer. In several such cases laparotomy has been carried out. It may generally be maintained that information relative to the condition of the lungs, more exact by roentgen examination than by any other methods, ought, in a greater extent than hitherto has been the case, to be included in the routine pre-operative schedule.

The following case which occurred in our clinic some time ago seems worthy of mention in this connection. The patient was a man of about 45, admitted by a well known internist, who for some time had treated the patient for abdominal symptoms, which on roentgen examination had been established as arising from cancer of the stomach. Nothing abnormal had been observed from the lungs on auscultation and percussion. Pre-operative roentgen examination of the lungs had not been done. The tumor was fairly easy to resect and the course was during the first post-operative days smooth. The patient had, however, a stubborn fever, which hardly was explicable for abdominal reasons, and in addition a stubborn post-operative cough. There were abundant râles but nothing suggestive of pneumonia. A roentgen was taken and revealed a widespread old bilateral pulmonary tuberculosis with walnut-sized caverns; there were abundant tubercle bacilli in the sputum. After a few weeks he was transferred to a sanatorium.

It is evident that the presence of a patient with open phthisis and numerous tubercle bacilli in his expectoration is not a negligible matter in a surgical ward.

It is of course true that in the foregoing consideration has been taken to the conditions in a *surgical department;* it is, however, presumable that

n a near future roentgen examination of heart, lungs, kidneys and abdominal organs will also in the medical clinics be carried out early, as soon as possible after admission, and at least in the chronic cases by routine in every patient.

Many factors seem to indicate that the development decidely and at an increasing pace follows this trend and that this development cannot be arrested by the fact that there still are those physicians who contend that such a development is not felicitous, in that an overestimation of the importance of roentgen examination and an underestimation of the usual diagnostic measures of clinical medicine thus ensues.

Many distinguished internists and mainly the chiefs of medical hospital departments, however, already embrace the opinion that the basis for a further perfection of the diagnosis which is afforded thanks to a roentgenologically based knowledge of the anatomy the physiology and eventually the pathological anatomy of the *heart, lungs, kidneys, gall-bladder, stomach and intestinal canal* is of great and indispensible importance.

The comprehension of the ever increasing value of roentgen examinations in clinical work with, as a consequence, the increased demands on the capacity of the roentgen departments is of no mean importance in planning new roentgen departments; those departments which now are built with consideration merely of the *present* requirements will with great certainty after the lapse of a very short time be seen to be inadequate. It would therefore seem to be rational to plan every new roentgen department in such a manner that there is a possibility of future expansion.

An objection has been raised against the increase of roentgen examination in our hospitals, above stressed as highly desirable, with the motivation that the method is expensive, and that great savings would be effectuated by the community if these examinations were reduced the utmost possible, or at least not increased. Against this opinion the following arguments may, among others, be advanced.

The initial cost of establishment of our active hospitals, particularly, the surgical special departments, is very high, as well as the cost of running them. It is therefore from the point of view of economy desirable to treat the patient for the shortest possible time in these establishments, where the daily expense at present never is less than 20 swedish crowns per day and patient; this might also be expressed as follows: that the capital invested in a large and costly hospital yields the better interest, the more patients per annum which are admitted and discharged cured, a sentence earlier propounded and successfully advocated by GÖSTA EHMANSSON. Nobody can deny that there in many diseases is no method of examination that as rapidly and as accurately leads to a correct diag-

nosis, and that many diagnoses, especially early ones, are possible thanks to roentgen examinations alone. Thus, assuming that roentgen examination is necessary in a great many cases, and that the average expense of nursing a patient is about 20 swedish cr. a day, it follows that a waiting period of but 5 days for a roentgen examination may imply an expenditure of 100 swedish cr. for the community, this often without benefit to the patient. Other examinations may of course occasionally be done in this period of waiting, but not in all cases. It thus appears as though a perfectly functioning roentgen department, adequate in size and with an adequate personnel, also from the standpoint of economy, ought to be of great importance in the efficient and economical administration of our hospitals.

Finally, the author wishes briefly to mention the shortcomings and sources of error of roentgen diagnostics.

It was stressed already above that the method at least in our country has attained such a degree of perfection that a negative result of a roentgen examination (*i. e.* without pathological findings), carried out lege artis, of perhaps especially the lungs, stomach, colon, kidneys, to some extent also the gallbladder, for the consulting physician has come to imply that these organs are healthy or at least that this assumption may be used as the basis for continued examinations — an extremely high testimonial for Swedish roentgenology. It is mainly thanks to the organization of our roentgenologists and their training, earlier planned and accomplished by GÖSTA FORSSELL that this proud goal has been attained; it is also this scrupulous exactitude which is fundamental in what has been stated above relative to the importance of the method in especially the surgical clinic. It is, however, in this connection reasonable to discuss the question of the reliability of roentgen diagnostics, especially in regards to those organs or organ systems discussed above. A phrase, coined in the childhood of roentgenology »roentgen never is false, although the roentgenologist sometimes may be so» may perhaps to some extent be justifiable. The correct interpretation of the pictures is not always easy; to this comes an important factor — not always sufficiently taken into consideration by the roentgenologically untrained — that a correct roentgen diagnosis demands pictures correctly taken, in the right directions, with due avoidance of obscuring tissues, and that, at least in certain examinations of especially the alimentary canal — diverse technical manipulations are frequently demanded in order to bring out the pathological-anatomical changes on the roentgen picture. It is also evident that the correct interpretation of the pictures demands a very intimate knowledge of the normal anatomy, as well as anomalies and deviations from the normal which may be rare but not pathological. Roentgenology is not and probably never will become so mechanized but that individual

skill and aptitude will assert themselves. There are those who become fast masters in this particular fields of medicine — others again do not.

It may, however, be asserted that erroneous diagnoses in roentgen examinations of especially the kidneys and the abdominal organs, particularly the digestive canal, are very rarely occurrent among the roentgenologists of our country. This is also valid in regards to the colon, which in the earlier days of roentgenology was considered to be extremely difficult of access for close analysis, as, by way of example, in the detection of small cancer tumors. As late as in the beginning of the 'thirties the roentgen colon cancer diagnosis was in Germany considered so uncertain that on clinical suspicion of this disease laparotomy was considered indicated even on negative roentgen examination. In a study carried out by the author in 1933, on a series of 106 roentgen examined cases of cancer of the colon from Maria Hospital (Professor ÅKERLUND) and the Serafimer Hospital (Professor LYSHOLM) there was not one instance of erroneous diagnosis.

True, it is not only conceivable but definite that colonic tumors of a cancerous nature under a certain size are not roentgenologically demonstrable. Where this border line lies is not definitely known: neither is it entirely dependent on the size of the tumor alone. Last spring at the Serafimer Hospital a cancer barely the size of a hazel nut was operated in the sigmoid flexure of a man of 76, after having been roentgenologically established in a colon examination actually intended to exclude cancer in a patient with an old colitis. Thus, there were in this case no clinical symptoms directly suggesting cancer. In another observation some years ago, also at the Serafimer Hospital, a very slightly larger tumor was diagnosed in the hepatic flexure, a random bleeding from rectum giving rise to this examination. It is evident that growths as small as these, which clearly reveal the great importance of roentgen as an early diagnosticum in the lesion in question, only are to be detected by a minute and detailed study of the mucosa of the entire colon, which again require the minimum utilization of obscuring contrast medium. (See FORSSELL's studies on the mucosa!)

Although — as will be evident from the foregoing — the modern roentgen diagnostics, such as is their development in this country, especially in regards to those organs discussed above, generally afford clear information relative to the clinical diagnosis and but seldom and in exceptional cases are misleading, there still remain — and this ought always to be kept in mind — such cases. In those cases in which the clinical picture and the roentgenological findings are not in agreement it should be remembered that the further management of the case ought not to be based on a possibly negative roentgen, but should be subjected to a renewed clinical judgment.

I would like to conclude this paper with citing three such cases. There are of course many more, also in our records, but these three seem to be sufficient as illustrations. Which roentgenologist of but a few decades ago could have dreamt that erroneous roentgen diagnoses would become so exceptional as to be worthy of mention in the literature?

1) A woman of 66 had since about 2 years had dull pains in the right renal region; for the last weeks a slight hematuria also; the urine showed a number of red cells. *Urography:* rather large kidneys, equal in size, excretion time of contrast normal. Both renal pelves urographically identical, of normal appearance. *Operation* because of the pain, revealed a normal sized right kidney and in hilus a resistance the size of a walnut which was seen to be due to a concrement the size of a filbert and composed of urates. This concrement was lodged in a kind of diverticulum or inflammatory thickened pocket posterior in the renal pelvis.

The concrement thus being a urate stone did not give any shadow on the roentgenogram. As the diverticulum was entirely filled out by the stone no filling defect was obtained of the in other respects normally formed and normally contrast-filled renal pelvis, this fully explaining the negative roentgen picture.

2) A man of 61 had for 15 years had occasional discomfort of ulcus type in the epigastrium. In 1931 and 1940 dietary treatment for ulcer in another hospital. May 9, 1943, explorative laparotomy also at another hospital, with the suspicion of ulcer. Preoperative roentgen negative, at operation no signs of ulcer. In July of the same year renewed operation at the same hospital with cholecystectomy, nothing abnormal in the gallbladder, the pains continued. The patient was now referred to the Medical Clinic of the Serafimer Hospital. Roentgen examination of the stomach and duodenum and motor-test meal at the Serafimer Hospital negative; it was, however, noted that bulbus duodeni was directed nearly straight backwards so that no satisfactory compression was obtained. *Operation*, because of the pain, showed that the stomach was normal. Bulbus duodeni also appeared and felt normal. But on palpation of the lower duodenum there was discovered in pars verticalis several centimeters from pylorus on the posterior wall a walnut-sized ulcer tumor issuing from a very shallow ulcer the size of a penny, which was not distinctly felt until on palpation of the bowel from the interior. A so-called palliative resection was done, after which the patient became free of symptoms.

This patient had thus been roentgen examined in two different hospitals without discovery of his lesion. The position of duodenum with the resulting difficulty of obtaining a compression thereof, as well as the very shallow character of the lesion, were the reasons for its not being roentgenologically established.

The indication for operation was in this case also the severe pains of the patient.

3) A man of 61 had since 1938 been treated for ulcus ventriculi in several periods; in the spring of 1942 a niche had been demonstrated in the lesser curve, rather high up on the stomach. The spring of 1946 increased complaints. Roentgen at the Red Cross Hospital (Chief: prof. ÅKERLUND) 5. 23, 1946 according to the report »on this occasion showed gastritic phenomena but no organic changes of ulcus or other types». He was referred to the Surgical Department of the Serafimer Hospital with the suspicion of biliary passage disease.

Roentgen examination of kidneys, biliary ducts and bowel showed nothing abnormal. On 6. 11 a renewed roentgen of the stomach was done at the Roentgen Department of the Serafimer Hospital (Chief: Prof. LYSHOLM) with the same negative findings as at the Red Cross Hospital.

At *operation* carried out because of the patient's pain, an ulcus tumor nearly the size of an egg with a niche the size of a hazel nut was established high up in the stomach proximal to cardia. After a typical resection the patient was discharged free of symptoms.

In this case roentgen examination of the stomach was done within a few days at the Roentgen Departments of the Red Cross Hospital and the Serafimer Hospital, with the Professors ÅKERLUND and LYSHOLM as chiefs, respectively. This is a guarantee that the examination in this case was performed lege artis and with recourse to the perhaps most outstanding roentgenological expertise of our day, not only in this country but also internationally speaking. Although a case of this type is extremely rare it is apparent that roentgen examination under certain circumstances may have a negative result even in the case of quite a large ulcer, in spite of an examination carried out lege artis. In this case clinical judgment, with special consideration of the severe pain of the patients, was decisive in the management of the case.

SUMMARY

The author points out that roentgen diagnostics as yet are in the phase of rapid development. Roentgen is now becoming a routine method of examination in that the internal organs of the majority of hospitalized patients are roentgen examined shortly after admission.

A further development of roentgen diagnostics in this direction will, by affording earlier and more certain diagnoses, augment the hospital capacity, thus bringing about considerable economies.

Swedish roentgen diagnostics of to-day are so reliable that erroneous diagnoses very rarely are encountered. They may, nevertheless, occur, and the author cites three instructive instances. In the event of a divergency between the clinical picture and the roentgen findings the case must be taken up for renewed consideration.

ZUSAMMENFASSUNG

Verf. betont, dass die Röntgendiagnostik noch immer in rascher Entwicklung begriffen ist. Sie beginnt eine Routineuntersuchungsmethode in dem Sinne zu werden, dass die inneren Organe der Mehrzahl der Patienten einer Krankenhausabteilung bald nach der Aufnahme röntgenuntersucht werden.

Eine in dieser Richtung entwickelte Röntgendiagnostik wird durch früher und sicherer gestellte Diagnosen die Kapazität der Krankenhäuser vermehren und hierdurch bedeutende Ersparnisse ermöglichen.

Die moderne schwedische Röntgendiagnostik ist so zuverlässig, dass Fehldiagnosen sehr selten sind. Immerhin können sie hin und wieder vorkommen, wovon Verf. drei lehrreiche Beispiele gibt. Bei mangelnder Übereinstimmung des klinischen Bildes und der Röntgenbefunde muss der Fall erneut geprüft werden.

RÉSUMÉ

L'auteur souligne que le radiodiagnostic ne cesse de se développer rapidement. Il est en train de devenir une méthode de routine, en ce sens que, dans un service hospitalier, les organes internes, de la plupart des malades, dès leur admission, sont examinés aux Rayons Roentgen. Un développement dans cette direction-là augmentera le rendement de l'hôpital grâce à un diagnostic plus précoce et plus certain, et permettra de la sorte des économies considérables. En Suède le radiodiagnostic moderne est si sûr que ses erreurs sont très rares. Il en survient cependant, aussi l'auteur en rapporte-t-il trois exemples instructifs. Lorsqu'il y a discordance entre le tableau clinique et les constatations radiologiques le cas doit être réexaminé.

LE CŒUR CHEZ LES CORPULENTS. QUELQUES DÉTAILS RADIOLOGIQUES[1]

par

T. Klason, D. M.

Dans leurs œuvres classiques H. VAQUÈS et E. BORDET ont toujours analysé et les masses totales du cœur et ses quatre cavités. Mais maintenant il y a la tendance dans cette partie de la radiologie d'abandonner l'analyse minutieuse et difficile des détails du cœur pour un calcul plus facile de sa masse totale et pour trouver la relation entre la totalité du cœur et la surface de la peau de l'individu.

On peut généralement dire que le cœur chez un homme corpulent est un peu plus grand que chez un maigre, d'abord parce que le premier est plus pléthorique et puis parce que le cœur chez lui est forcé à un travail plus dur. En observant les gras on remarque facilement qu'ils ne sont pas comme gonflés entièrement: chez les uns le ventre est trop grand, chez d'autres les arrières, d'autres encore ont les joues gonflées etc. Si cette tendance du gras de s'accumuler à differentes places dépend d'une diète particulière ou est une trace héréditaire ou une specialité de la race on l'ignore. Dans la folklore on prétend que les differents aliments souvent donnent un aspect different. Chez les individus ordinaires on peut aussi observer quelque fois que certains parties de leur corps sont gras, par exemple le fameux double menton.

Le cœur est plus ou moins entouré de graisse, accumulée spécialement vers la pointe. Dans le pericarde il y a aussi beaucoup de graiss surtout derrière le sternum et vers la gauche où elle peut former une sorte de masse en forme de chou-fleur dans l'angle entre le cœur, le poumon et le diaphragme. Ces masses peuvent mesurer plusieurs centimètres en épaisseur, (voir Fig. 1 a et 1 b), et on doit penser à cela en calculant la grandeur du cœur.

Analysons maintenant six cas:

1. homme, 21 ans, longeur 183 cm., poids 112 kg.
   beaucoup de gras entre le sternum et le cœur (Voir Fig. 2 a et 2 b).

[1] Remis à la Réd. 1. 6. 1947.

Les masses de son cœur, en cm³, calculées selon A. KAHLSTORF, et ce chiffre en relation avec la surface de la peau de l'individu sont 730/315 sans le gras, 970/420 avec le gras.

3. homme, 34 ans, l. 181 cm., p. 111 kg., gras en avant et entourant aussi le cœur entier.
Le cœur 800/350 sans le gras; 970/420 avec le gras.

3. femme, 54 ans, l. 162 cm., p. 71 kg., la pointe du cœur entourée de gras, voir le cliché. (Fig. 3.)
Le cœur 600/345 sans le gras; 720/410 avec le gras.

4. femme, 64 ans, l. 165 cm., p. 65 kg., la pointe du cœur entourée de gras.
Le cœur 600/350 sans le gras; 700/410 avec le gras.

5. homme, 70 ans, observé depuis 1934.
1934 l. 170 cm., p. 71 kg. La pointe entourée de gras,
Le cœur 700/390 sans le gras; 830/460 avec le gras.
1937 l. 170 cm., il pèse maintenant 78 kg.
Le cœur 760/400 sans le gras; 1050/550 avec le gras.
1946 l. 170 cm., p. 71 kg.
Le cœur 740/390 sans le gras; 980/540 avec le gras.
On observe que pendant ces 12 années son poids a augmenté et diminué de 7 kg. Le cœur a gardé à peu près sa masse musculaire, y compris son sang, et aussi sa relation à la surface de la peau. Les masses grasses entourant le cœur ont augmenté avec le poids mais une fois fondues elles ont eu la tendance de rester à leur place.

6. homme, 50 ans, le cœur est entouré de gras en avant et vers la gauche.
1937 l. 174 cm., p. 78 kg.
Le cœur 780/405 sans le gras; 900/510 avec le gras.
1941 l. 174 cm. p. 69 kg.
Le cœur 790/430 sans le gras; 900/510 avec le gras; 1150/600 le gras entre le cœur et le sternum y compris.

Cet individu a maigri mais le cœur garde sa grandeur musculaire, les masses grasses autour du cœur restent aussi inalterées quand il perd 9 kg. On doit aussi noter la différence entre les deux calcules 790 et 1150 indiquant la grandeur du cœur sans et avec le gras.

Conclusion

Les masses grasses qui entourent le cœur sont cardiaques et pericardiaques. Chez les individus plus jeunes le gras s'accumule souvent

Fig. 1 a.

Fig. 1 b.

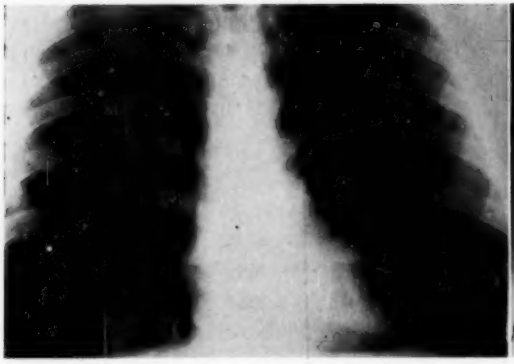

Fig. 2 a.

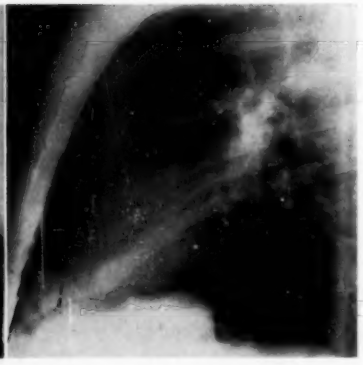

Fig. 2 b.

Fig. 1 a. La cage thoracique ouverte d'une femme de 73 ans et d'une stature ordinaire. Le poumon gauche est poussé en arrière. On voit le cœur entouré par beaucoup de graisse, accumulée surtout à la surface exterieure du péricarde et entourant ainsi la pointe du cœur. On observe que le gras, ici presque seulement péricardiaque, enveloppe la pointe du cœur. Le × marque la pointe du cœur.

Fig. 1 b. Le même cas. Un coup frontal par la pointe du cœur et le péricarde. Le gras, ici presque seulement péricardiaque, enveloppe la pointe du cœur. Voir fig 3 où ce gras est visible comme une zone demitransparente entre le cœur et le poumon gauche.

Fig. 2. Cas I, homme, 21 ans, très corpulent. Le gras est accumulé surtout entre le sternum et le cœur.

Fig. 3. Cas III, femme, 54 ans, un peu corpulente. Beaucoup de gras à la gauche.

plus en avant mais avec l'âge aussi à gauche entourant la pointe du cœur. Ce gras a la tendance, une fois fondu, d'y rester tel, quand l'individu maigrit. Le cas nr 3 indique que le cœur peut être entouré par beaucoup de gras même chez un individu ordinaire. En vérité le gras cardiaque et péricardiaque formait 16 % du poids de son cœur. Chez le nr. 5 le pourcentage s'élevait à 38.

RÉSUMÉ

L'auteur indique que le cœur est entouré de graisse, soit cardiaque soit pericardiaque. Ce gras peut même chez des individus ordinaires obtenir beaucoup d'épaisseur. Le gras a la tendance avec l'âge de s'accumuler autour de la pointe du cœur et y rester. En calculant la grandeur du cœur on doit indiquer si le gras est inclu ou non dans le calcul.

SUMMARY

The author points out that the heart is surrounded by fat, either cardiac or pericardiac. This fat can even in ordinary persons attain a considerable thickness. With age the fat has a tendency to accumulate around the apex and remain there. In calculations of the heart-volume it ought to be stated if the fat is included or not.

ZUSAMMENFASSUNG

Verf. macht darauf aufmerksam, dass das Herz von Fett umgeben ist, sei es Herzfett oder Perikardialfett. Dieses Fett kann sogar bei normalen Personen bedeutende Dicke erreichen. Mit zunehmendem Alter neigt das Fett dazu, sich um die Herzspitze herum anzusammeln und dort liegen zu bleiben. Bei der Berechnung der Herzgrösse ist anzugeben, ob das Fett mit einberechnet ist, oder nicht.

FROM THE GYNECOLOGICAL DEPARTMENT (CHIEF: PROFESSOR ERIK RYDBERG), AND THE ROENTGENOLOGICAL DEPARTMENT (CHIEF: PROFESSOR FLEMMING MØLLER) OF THE RIGS-HOSPITAL, COPENHAGEN

HYSTEROSALPINGOGRAMS IN GENITAL TUBERCULOSIS IN WOMEN[1]

by

Valdemar Madsen

The clinical diagnosis of genital tuberculosis in women is difficult. In his work of 1944 on gynecological tuberculosis, HANS THOMSEN says: »Even on employment of all modern diagnostic adjuvants, in a not inconsiderable number of cases it will be impracticable with merely a fair degree of certainty to make a clinical decision. In this field, therefore, a broad margin has to be left for the explorative measures — laparotomy as well as uterine curettage.»

As is well known, the demonstration of salpingitis in a virgin is highly suggestive of tuberculous salpingitis. Furthermore, the concurrence of oligohypomenorrhea, sometimes amenorrhea, with clinical demonstrable salpingitis is a constellation which likewise is somewhat suggestive of a tuberculous origin of the salpingitis.

With the increasing sterility examination, genital tuberculosis has been revealed in an increasing number of cases through the circumstance that tuberculous endometritis has been demonstrated accidentally on the endometrial biopsy that constitutes a natural link in such examinations. Thus it has been realized that genital tuberculosis in women undoubtedly occurs more frequently than assumed before.

It is also to be mentioned that the examination of the vaginal secretion by cultivation for tubercle bacilli as recommended by HANS THOMSEN has disclosed several instances of genital tuberculosis that would not otherwise have been diagnosed.

The aim of the present paper is to show which types of roentgenograms are obtained by hysterosalpingography on patients in whom the genital tuberculosis has been verified by laparotomy or endometrial biopsy.

The present work further aims to show that with our present knowledge concerning the interpretation of the pictures obtained, hysterosalpingo-

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salpingography has revealed the presence of genital tuberculosis in a number of women whose symptoms often were vague and by no means suggestive of tuberculosis, while often the only complaint of the patient was her sterility — and also often in cases where the ordinary gynecological examination showed no abnormality.

In working up the material for my dissertation (1942) I had occasion to see a few cases of salpingitis in which the tubal passage was blocked at the abdominal ostium, while, in spite of this closure the tubes were dilated a little or not at all — in contrast to what is usually seen in roentgenograms of sactosalpinges.

In one of these cases the patient was found to have genital tuberculosis. In another case the patient had tuberculous pleurisy, and thus my attention was called to the possibility that tuberculous salpingitis perhaps might be assumed to present this characteristic salpingogram with retention of the contrast medium in tubes that were dilated but only in a very moderate degree or not at all.

The further salpingographic studies have shown that just these salpingographic features were encountered in a number of cases where the diagnosis of genital tuberculosis subsequently was verified operatively. But, also other types of roentgenograms were obtained from patients with tuberculosis, and in the following an account will be given of these hysterosalpingographic findings.

In 9 patients with histologically verified genital tuberculosis the following type of salpingitis was demonstrated hysterosalpingographically. After injection of the contrast medium the tubes are slightly flask-shaped, dilated only in a moderate degree or not at all, and the contrast medium is retained in the tubes on roentgenography 24 hours after the injection. The pictures may vary somewhat but on the whole they are of the type shown in Figs. 1 and 2.

In these 9 patients (Record Nos. 590/43, 723/43, 301/45, 221/46, 825/46, 878/46, 56/47, 279/47, amb. A. L.) the genital tuberculosis was verified by histological examination of the removed adnexa or of the endometrium (in 4 of the 9 cases). In the four cases where the genital tuberculosis was verified only by endometrial biopsy, however, the presence of salpingitis was unquestionable. So it seems reasonable to reckon that, like the endometritis, the salpingitis was of tuberculous nature too.

In 4 patients (Record Nos. 643/44, 149/45, 380/45, 507/46) with clinically definite genital tuberculosis, all of whom were treated operatively, and in whom the diagnosis was verified by microscopy, hysterosalpingography showed a somewhat greater dilatation of the tubes — similar to the dilatation sometimes encountered, for instance, in gonorrheal hydrosalpinges. Naturally, no sharp borderline can be drawn between the cases in which the tubes are not dilated, and the cases forming distinctly

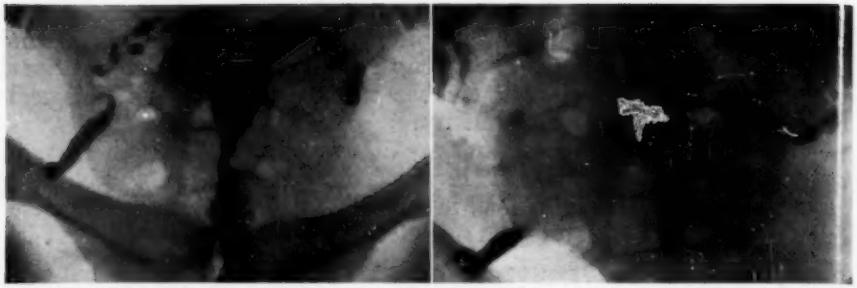

Fig. 1.

Fig. 2.

dilated sactosalpinges. So, sometimes it will be a matter of judgement whether the roentgenograms are to be in one or the other of these two groups. In general, I think, it may be safe to reckon with the thickness of a lead-pencil at the widest part of the tube as the limit. Whenever I have estimated sactosalpinges as not — or practically not — dilated, they seldom have exceeded the thickness of a slate-pencil.

In cases where the tubes have been more dilated we sometimes have seen a simultaneous process of calcification in the tube, so that the contrast medium has been deposited round this calcified area. This combination gives rise to pictures with characteristic features owing to the simultaneous presence of contrast oil and lime salts. For illustration of this it will be appropriate to cite the following case history.

Case 1 (Record No. 533/45). Married woman, 32 years old.

Complaints: Primary sterility; periodical abdominal pain that may be elicited by cold and during coitus.

Past history negative as to tuberculosis.

Gynecological examination: External genitals, vagina and portio vaginalis apparently

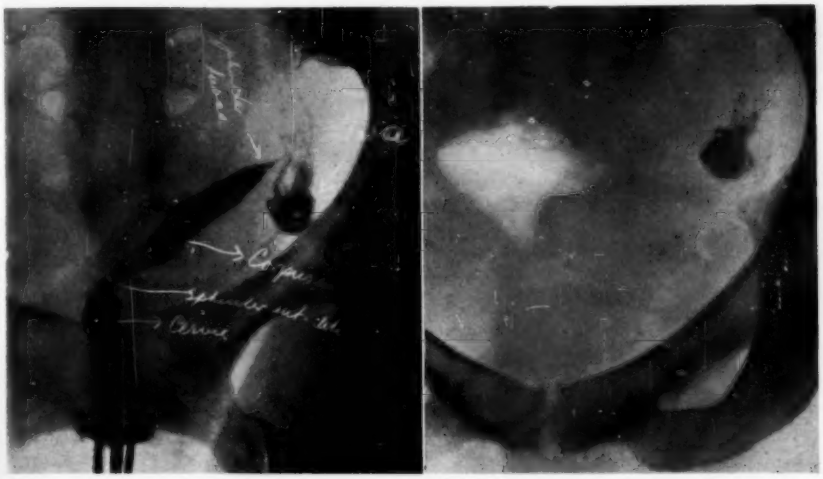

Fig. 3.

normal. Sinistroposition of the uterus, of normal size, fairly mobile. Corresponding to the left adnexa and parametrium, slight thickening, tension and tenderness.

Endometrical biopsy: Normal ripe secretory phase without any sign of tuberculosis.

Hysterosalpingography (Fig. 3): Filling only of the left part of a completely bilocular uterus and of the corresponding tube. Here the contrast pattern is irregular shagreened. 24 hours later: Roundish contrast shadow retained in the left sactosalpinx. Density of the shadow not homogeneous, reminding of a ball of woollen yarn.

Laparotomy: Right horn of the uterus rudimentary. Right tube rudimentary, 3—4 cm. long, with small rudimentary fimbriae. Left part of the uterus a little smaller than normal; left sactosalpinx, a little thicker than a lead-pencil except for the uterine end (about 2 cm.); tiny remnant of an orifice corresponding to the abdominal ostium, barely admitting a probe, which meets with a hindrance just inside the minimal ostium. This hindrance is due to the filling of the tubal lumen with calcified, almost stony, masses. In the mesosalpinx, near the ovary a calcified lymph gland, twice as large as a millet seed.

Microscopic diagnosis: Tuberculous salpingitis.

A similar picture is seen in Fig. 4, with the contrast medium retained in a calcified tube, giving the shagreened pattern that has to be attributed to the simultaneous presence of deposited lime salts and the contrast oil retention. Also this patient was submitted to laparotomy. Opening of the tube revealed its calcium content. Microscopic examination showed typical tuberculous salpingitis (Record No. 216/46).

In this connection, a third case has to be mentioned, likewise with areas of calcification in the tuberculous salpingitis.

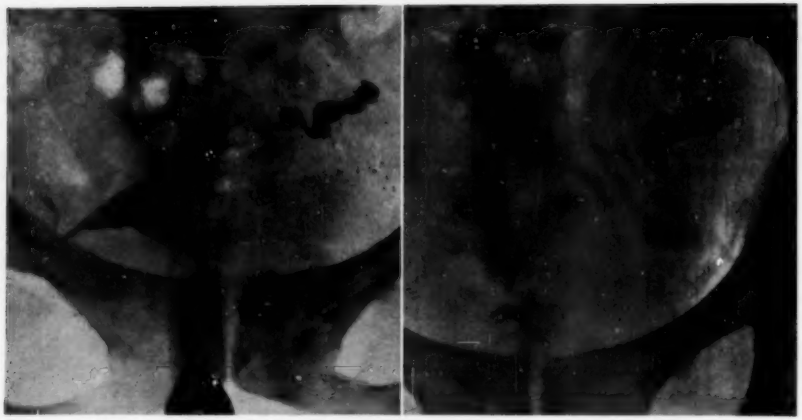

Fig. 4.

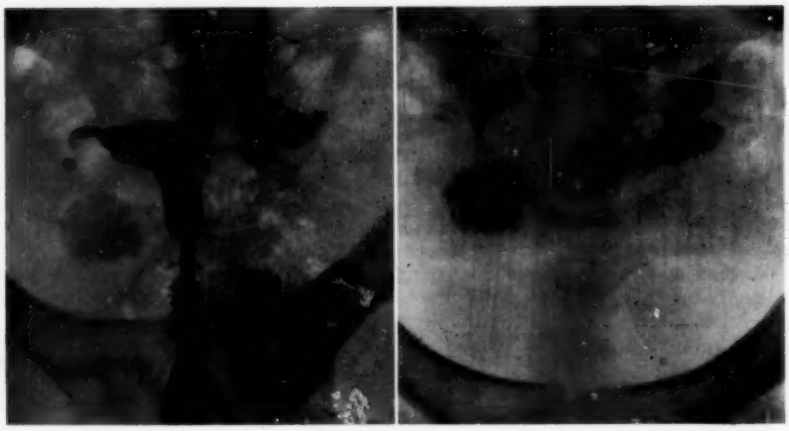

Fig. 5.

Case 2 (Record No. 852/46). Married woman, 29 years old.

7 years before: Laparotomy for ileus (division of adhesions). Cultures from the peritoneum: + TB.

Complaints: Primary sterility. No other complaints.

Gynecological examination: Slight retroposition of the uterus, which otherwise appears normal. To the right of the uterus a cherry-sized, firm, indolent intumescence, which on exploration resembles a small fibroma (and probably is the calcified tube).

Hysterosalpingography (Fig. 5): Only the uterine sections of the tubes are filled with contrast medium, both have a wider caliber than normal. A little laterally to the stunted

Fig 6.

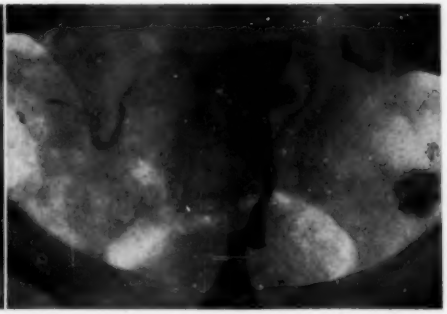

Fig. 7.

tubes, on either side a mosaic-like roundish contrast shadow is seen, the right like half and almond, the left as large as a grape. These shadows are seen also on roentgenograms taken 24 and 48 hours after.

Endometrial biopsy: Tuberculous endometritis.

No treatment; in particular, no operation performed.

Discussion. — The mosaic-like, shadow-producing formations lateral to the stunted contrast-filled salpinges might conceivably originate from the retention of contrast medium in large sactosalpinges from previous hysterosalpingography. The patient claimed most decidedly, however, that she never had submitted to hystersalpingography before. So the only remaining possibility is that these shadows come from processes of calcification in the tube, and this is quite in keeping with her past history (peritoneal tuberculosis), with the abnormal filling of the tubes and with the outcome of the endometrial biopsy (tuberculous endometritis).

So, even though no laparotomy was found on this patient, the diagnosis was established as tuberculous salpingitis with calcification.

Such processes of calcification may occur also in the abdominal lymph glands. When the calcifications here are encountered in patients in whom the roentgenograms showed typical salpingitis, it is obvious to assume that the salpingitis is of tuberculous nature. Examples of this are seen in Fig. 6 (Record No. 808/43) and Fig. 7 (Record No. 129/46).

In the present material, only one case presented a picture of retention of contrast medium in the tubes combined with a simultaneous fairly copious evacuation into the peritoneal cavity. Generally, the tubal changes in tuberculosis may be assumed to be so considerable that passage of the contrast medium stops or at any rate is reduced to a minimum.

Fig. 8 (Case Record No. 56/52) shows the pictures of the case just mentioned in which tubal retention was combined with a considerable evacuation into the peritoneal cavity. Even though it cannot be said

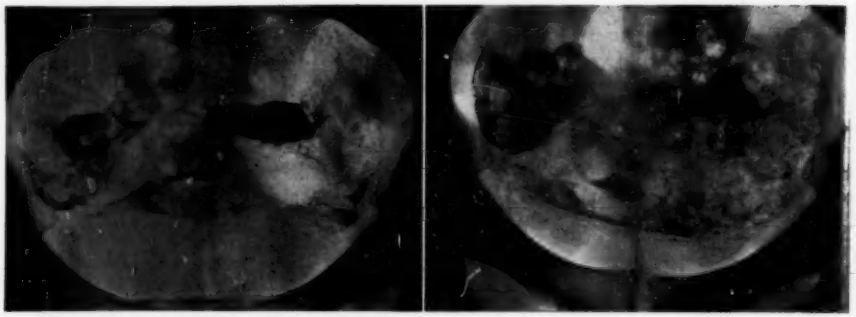

Fig. 8.

to have been proved positively that the salpingitis in this case was of tuberculous nature, this is still most likely, partly because of the past history of the patient (previous open pulmonary tuberculosis, previous operation for chronic appendicitis) and especially on account of endometrial biopsy which showed a tuberculoid inflammation.

Now the only complaint of the patient was sterility.

This is the only case in our material in which the tubes were distinctly dilated and at the same time presumably constricted at the abdominal ostium; and yet they permitted an abundant evacuation of contrast medium into the peritoneal cavity; and this case will serve to illustrate that all salpingographic forms of salpingitis may be encountered also when the salpingitis is of tuberculous character, even though, judging from this material, the types described before this one are to be looked upon as being by far the most frequent.

In tuberculous salpingitis, as is well known, the walls of the tubes often undergo quite considerable changes. So it is not to be wondered that in a few cases no contrast medium is allowed to enter the tubes on hysterosalpingography, the tubal passage being blocked at a place corresponding to the uterine orifice. This has occurred in two cases.

In one of these cases (amb. J. K.), contrast medium was forced into the uterine musculature, as not sufficient regard was paid to the blocking of the tube and the resulting resistence of the injection. In this case endometrial biopsy showed typical tuberculosis. The patient was not given any treatment — in particular — not operative — but the diagnosis of tuberculous salpingitis still has to be looked upon as almost established.

In the other case (Rec. No. 566/42) salpingo-oophorectomy was performed. Microscopic examination showed endosalpingitis, here and there suspect of specific inflammation.

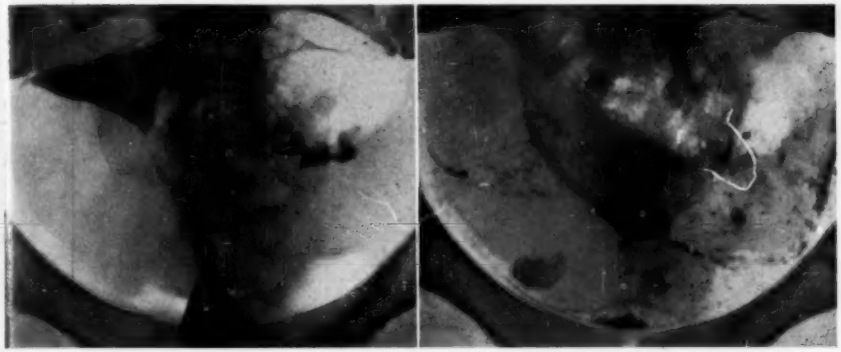

Fig. 9.

These remarks on the complete absence of tubal filling in two cases of tuberculous salpingitis are not to be taken to mean that the failure of tubal filling would just be a sign of genital tuberculosis. Occlusion of the uterine ostium of the tube may occur in any etiological form of salpingitis and also in lesions of other internal genitals. Sometimes a defective filling of the tube may simply be due to the circumstance that the examinatoin has been defective technically — the contrast filling in the uterine cavity being too scanty.

Among the changes observed on hysterosalpingography in patients with genital tuberculosis, mention is yet to be made of the hysterosalpingographic picture of ascites and of extensive changes in the uterine mucosa.

C a s e 3 (Record No. 362/46). Married woman, 26 years old.

Complaints: Primary sterility.

Two years before, metrorrhagia of relatively short duration, treated with currettage. Since then, perfectly normal menstruation, 4 days/1 month.

Gynecological examination showed no abnormality.

Hysterosalpingography: Slight dextroposition of the uterus which otherwise appears normal. Blocking of the right tube at the uterine orifice. Continuous filling of the left tube without any distinct dilatation, and with evacuation of the contrast medium as globules into the peritoneal cavity. Roentgenography, 24 hours later: Abundant evacuation into the peritoneal cavity, forming close-lying globules and coarse plaques — as seen on increase in the amount of fluid in the pelvis.

Explorative laparotomy: Abundant amount of fluid in the peritoneal cavity; omentum markedly fleshy, infiltrated and adhering to the uterus and adnexa; the small intestine showing miliary tuberculosis. The adhesions round the right adnexa are detached readily. Now the tube looks red, slightly thickened, with patent abdominal ostium. The left adnexa is left intact as obviously the tuberculous process is so extensive throughout the abdominal cavity that any operative treatment is out of the question.

Microscopy of a piece of the omentum: Tuberculosis.

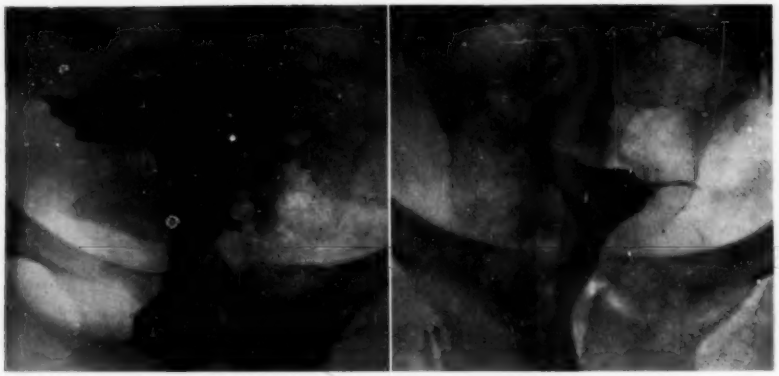

Fig. 10. Fig. 11.

Two patients presented distinct pictures of tuberculous endometritis, which here must have been rather extensive. For it is to be emphasized that tuberculous changes in the endometrium generally do not develop so far that they may be reckoned to appear in the hysterogram. These pictures are shown in Figs. 10 and 11.

Case 4 (Record No. 406/43). Married woman, 37 years old.

Past history of pleurisy and tuberculosis of one eye, requiring removal of the eye. Present complaints: Secondary sterility. Menstruation varying in intensity, sometimes very slight, sometimes profuse, and sometimes of ordinary character, now and then accompained by pain localized to the left iliac fossa.

Gynecological examination: Retroposition of the uterus, which is slightly enlarged, feeling somewhat »granular» on the posterior surface, but without fibromas. Semisolid, plum-sized, moderately tender intumescence in the left adnexa.

Hysterosalpingography (Fig. 10): Enlargement of the uterine cavity with very irregular — in several places dentate — contours; no clearing in the filling; no filling of the tubes.

Treatment: Laparotomy with total hysterectomy and bilateral salpingo-oophorectomy.

Microscopy: Tuberculous endometritis and myometritis; bilateral tuberculous salpingo-oophoritis.

Case 5 (Record No. 711/44). Married woman, 44 years old.

Complaints: Oligohypomenorrhea.

Histological examination: No abnormality.

Hysterosalpingography: Uterus of normal size. Corresponding to corners of the uterus the contours are irregular. Only the first part of the left tube is filled. Otherwise no contrast medium in the salpinges.

Endometrial biopsy: Tuberculous endometritis.

No operative treatment.

Now we have gone through the hysterosalpingographic pictures under which the genital tuberculosis — especially tuberculous salpingitis — has manifested itself in our material. It is to be emphasized that even though there is probably no absolutely specific roentgenogram for tuberculous salpingitis, according to my observations the following features still are strongly indicative of the tuberculous nature of the lesion: 1) when the abdominal ostium is closed the tube is often considerably less dilated than in other etiological forms of sactosalpinges; 2) sometimes areas of calcification are seen in the tube too; 3) in some cases calcified lymph glands are seen in the pelvis too.

The few cases in which the tubes are not filled tell us nothing about the etiology of the underlying salpingitis.

I have gone through the material in this department of patients who were operated after hysterography, and here I have not found anything to invalidite the observation that retention of the contrast medium in tubes which are dilated but slightly or not at all is highly suggestive of a tuberculous origin of the salpingitis, whereas retention in dilated tubes is the most frequent form of sactosalpinx formation when the salpingitis is of gonorrheal or septic origin. In the material reported in my previous work there were four cases of retention in non-dilated tubes, and in two of these cases the lesion was most likely of tuberculous nature. In the remaining two cases on the other hand, hysterosalpingography was performed very soon after the markedly acute onset of the salpingitis with fever, pronounced intumescence and increased sedimentation rate. No cases of this character are included in the present material simply because now we never perform hysterosalpingography in the acute or subacute phase of salpingitis, but only when this lesion takes a distinctly chronic course. It is not improbable that the retention of the contrast medium in the two cases of non-tuberculous salpingitis, in which the examination was performed very soon after the acute state, presented the mentioned appearance just because the sactosalpinges have not had time to reach the chronic stage with the greater dilatation characteristic of this.

Generally it is hardly to be expected that the tuberculous endometritis will disclose its presence on roentgenography. For this requires pronounced changes, and the pictures obtained in such cases may hardly be said to be typical of the tuberculous character of endometritis.

The acquaintance with these roentgenological features has made it possible for us to diagnose several cases of genital tuberculosis which otherwise might not have been recognized. The present material comprises altogether 20 cases in which the diagnosis of genital tuberculosis has been verified histologically and 22 cases in which the same diagnosis has been most probable, but no verified histologically. In this total of

42 cases the picture of more or less retort-shaped tubes, dilated but slightly or not at all was encountered in 29. The picture of retention in more dilated sactosalpinges was seen in 8 cases, 3 of which showed also areas of calcification in the tubes, and others showed calcified abdominal lymph glands.

The combination of tubal retention of contrast material and passage of such material into the peritoneal cavity was found only in one case. Lack of tubal filling occurred in 4 cases, among which the state of tuberculous endometritis was plainly evident roentgenographically in 2. Finally the picture of tuberculous ascites was seen in one case.

In the 22 cases where no final decision was made in the form of histological examination, at any rate the presence of salpingitis was established, and for the above-mentioned reasons this salpingitis was most likely of tuberculous nature. Furthermore, on thorough questioning, 17 of these 22 patients were able to furnish the information that previously they had had other manifestations of tuberculosis.

It has not been the aim of this paper to give any survey of the clinical aspects of the cases here described.

As mentioned in the introduction, however, it is to be emphasized that in several of these cases it would not have been possible to make the diagnosis without the employment of hysterosalpingography. For one thing, in several cases we should not have been able to demonstrate the presence of salpingitis, the explorative findings being uncertain or even negative. Furthermore, in several cases we should not have expected the lesion to be just of tuberculous character — in the absence of any general clinical evidence of such infection. (There was no virgin in this patient material, and among the 20 histologically verified cases, 6 patients were unable to give any information about previous tuberculous manifestation.)

In all these cases, thus hysterosalpingography has been of considerable significance both with regard to the establishment of the presence of an inflammatory process in the genitals, and also with regard to calling attention to the circumstance that the inflammatory process might be tuberculous.

SUMMARY

A survey is given of the hysterosalpingographic features encountered in 42 patients with histologically verified genital tuberculosis (20 patients) or with non-histologically verified but otherwise highly probable genital tuberculosis (22 cases). Description is given of the typical roentgenograms. The most frequent picture is that of sactosalpinges without any marked dilatation (29 cases). Sometimes areas of calcification are seen in the tubes or abdominal lymph glands. Individual pictures of tuberculous endometritis and tuberculous ascites are described. The significance of hysterosalpingography to the diagnosis is pointed out.

ZUSAMMENFASSUNG

Es wird eine Übersicht gegeben von den hysterosalpingographischen Befunden, die an 42 Kranken teils mit histologisch bestätigter Genitaltuberkulose (20 Fälle), teils mit histologisch nicht bestätigter, aber sonst sehr wahrscheinlicher Genitaltuberkulose (22 Fälle) erhoben wurden. Die typischen Röntgenogramme werden beschrieben. Am häufigsten findet man das Bild einer Saktosalpinx ohne ausgesprochene Erweiterung (19 Fälle). Manchmal sieht man in den Tuben oder den abdominalen Lymphdrüsen verkalkte Bezirke. Individuelle Bilder von tuberkulöser Endometritis und tuberkulösem Aszites werden beschrieben. Die Bedeutung der Hysterosalpingographie für die Diagnose wird betont.

RÉSUMÉ

Compte-rendu des constatations hystéro-salpingographiques faites chez 42 malades atteintes de tuberculose génitale vérifiée histologiquement (20 cas) ou de tuberculose du même ordre non prouvée par le microscope mais par ailleurs hautement probable (22 cas). Description des radiographies typiques. L'image la plus fréquente est celle de sactosalpinx sans aucune dilatation accentuée. Parfois on voit des aires de calcification dans les trompes ou les ganglions lymphatiques abdominaux. L'auteur décrit des images individuelles d'endométrite tuberculeuse et d'ascite bacillaire. Il souligne le rôle diagnostique de l'hystéro-salpingographie.

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FROM THE ROENTGEN-DIAGNOSTIC DEPARTMENT II OF SÖDERSJUKHUSET, STOCKHOLM, SWEDEN (HEAD: W. MAGNUSSON, M. D.)

FURTHER EXPERIENCES IN THE ROENTGEN DIAGNOSIS OF TUBERCULOUS SALPINGITIS[1]

by

W. Magnusson, M. D.

Hysterosalpingography (HSG) has acquired increasing importance in the analysis of the causes of female sterility. In spite of the large and wide-spread experience with this examination it has hitherto been used almost exclusively for investigating the patency of the Fallopian tubes and very little interest has been devoted to the study of the roentgenographic appearance of the tubes themselves after different types of salpingitis. It is generally accepted that HSG can only be performed after the inflammation has subsided and that the roentgen appearances after different types of infection are the same, so that it is impossible to distinguish between them. (1, 2, 3.) With our present knowledge this opinion seems to be correct as far as gonorrhoea and septic infection of the tubes and of the pelvic peritoneum are concerned. In 1939, PHILIPP and HUBER (4) stated that tubal endometriosis often gives a characteristic roentgen picture and this finding was later confirmed by MADSEN (5). ÅKERLUND (6) has described similar changes in endometriosis of the uterus. In a previous paper (7) the author has given an account of a study of the roentgenographic picture in 12 cases of tuberculous salpingitis. This study stressed the fact that an active tuberculosis often existed in the tubes without any clinical signs of disease being present. In these cases the tubes often showed finely jagged and ragged contours with small lumen-defects and sometimes also abscess- and fistula-like extensions from the lumen. As these changes were not present in other cases the author concluded that it was possible to diagnose tuberculous salpingitis by HSG in the majority of instances.

In this paper a report of additional cases is given where the diagnosis has been confirmed histologically and further experiences from the whole material are described.

[1] Submitted for publication, May 21, 1947.

Case 1. HSG 12. 5. 1942. Fig. 1. The tubes are widened, especially in the periphery, where the contours in several places show the typical jagged and ragged appearance. This characteristic picture is also clearly visible on a film, taken 24 hours afterwards. None of the contrast medium has passed out into the peritoneal cavity. Fig. 2.

The patient was operated on in another hospital in February 1945. Histological examination: In the left tube extensive tuberculous changes with numerous tubercles containing epitheloid cells and giant cells of Langhans type. In places tubercles also present in the subserous tissue. Tubal tuberculosis.

Case 2. HSG 16. 3. 1944. Fig. 3. Both tubes are widened especially in the periphery and show straight contours. At both ends there are small sacs with unhomogeneous contrast content. No passage into the peritoneal cavity.

Operation 13. 4. 1944. Many adhesions in the true pelvis. Both tubes closed and thickened with saccular dilatations at their ends. The distal end of the right tube was removed.

Histological examination: The tube shows pronounced chronic inflammatory changes with many collections of epitheloid cells in the granulation tissue. Some of them contain giant cells of Langhans type. The histological picture resembles tuberculosis. Tbc-bacilli have not been found but in all probability tuberculosis is present.

Case 3. HSG 17. 7. 1942. Fig. 4. Both tubes widened. Their central parts are somewhat straight and show even contours. Peripherally the contours are uneven. No passage into the peritoneal cavity. Unhomogeneous contrast content after 24 hours.

Operation 8. 12. 1943. Both tubes stenosed just internal to the fimbriae with thickening medially.

Histological examination: Adhesions and almost total obliteration of the tubal lumen with granulation tissue containing tubercles, giant cells of Langhans type and necrotic areas. On the left side also chronic non-specific inflammation. Tuberculous salpingitis.

Case 4. HSG 4. 6. 1945. Fig. 5. Both tubes are widened at the periphery and show even, but somewhat straight and rigid contours, especially on the left side. No contrast medium passed out.

Operation 18. 7. 1945. Both tubes were blocked, hard and nodular. In the report from the operation nothing is mentioned about suspected tbc.

Histological examination: In the left tube several histologically typical tubercles with giant cells of Langhans type. Some of these tubercles show caseous necrosis, others more or less fibrosis. In the outer layers of the wall there are in places typical tubercles. Tuberculous salpingitis. No bacilli found. The wall of the right tube is thickened and hard with sparse collection of inflammatory cells here and there. No tuberculosis visible.

Case 5. HSG 5. 11. 1945. Fig. 6. Only the central parts of the tubes are filled with contrast medium. The left tube is somewhat straight in its appearance and slightly widened peripherally. The contours are even. No contrast medium passed out. After 24 hours, a sac, the size of a hazel-nut with unhomogeneous contrast content is seen.

Operation 9. 11. 1945. Both tubes are closed, thick and finely nodular. In the report nothing is said about suspected tuberculosis.

Histological examination: Right tube: The wall shows clearly a chronic inflammatory process with complete obliteration of the lumen. The granulation tissue has as a rule a rather non-specific appearance, but in some places histologically typical tubercles with giant cells of Langhans type and central caseous necrosis are found. The left tube shows

Fig. 1. Case 1.

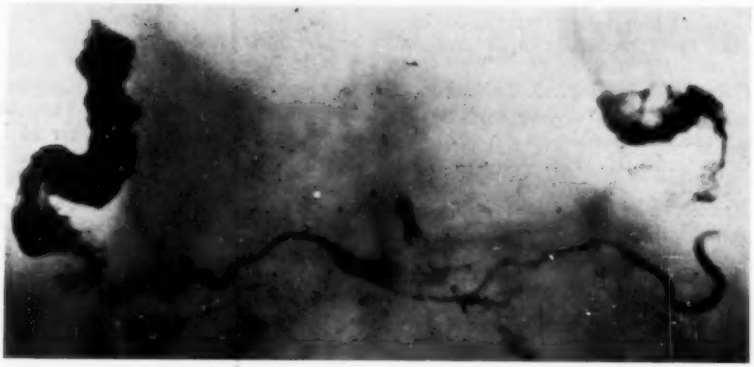

Fig. 2. Case 1.

Fig. 3. Case 2.

Fig. 4. Case 3.

Fig. 5. Case 4.

Fig. 6. Case 5.

Fig. 7. Case 6.

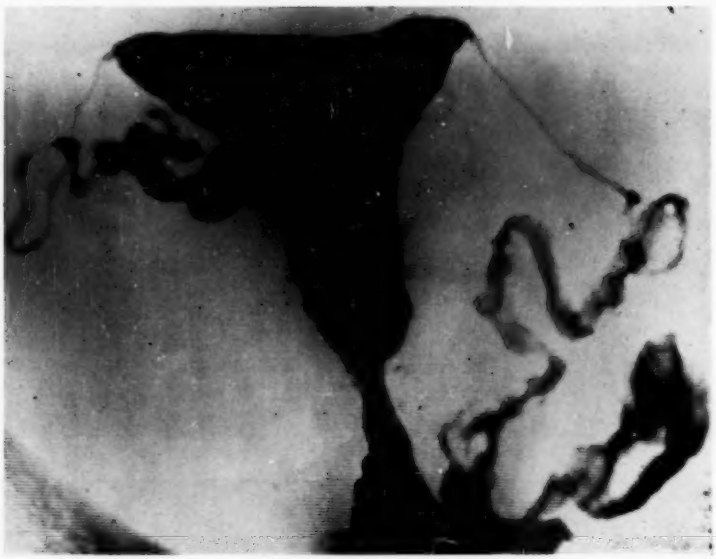

Fig. 8. Case 7.

similar changes. A part of this tube shows a cystic dilatation filled with caseous necrotic masses. Otherwise the lumen is obliterated. Tuberculous salpingitis.

Case 6. HSG 4. 6. 1946. Fig. 7. Both tubes are widened in the periphery and show straight and rigid but even contours perhaps with some fine waves near the end on the right side. Both ends are widened to form small sacs with unhomogeneous contrast content. No passage into the peritoneal cavity.

Operation 25. 11. 1946. Both tubal ends thick and hard, medially a few pea-sized hard nodules. No macroscopic signs of tbc.

Histological examination: The folds of the mucous membrane are in both tubes adherent to each other, forming a network. In the stroma several histologically typical tubercles of epitheloid cells often containing giant cells of Langhans type are found. In places signs of caseous necrosis. In the outer layers of the walls some tubercles and collections of inflammatory cells, for the most part lymphocytes. No bacilli found. In all probability tuberculosis.

Case 7. HSG 8. 10. 1946. Fig. 8. Both tubes are well filled with contrast medium, peripherally widened and show here very clearly jagged and ragged contours with lots of small uneven defects in the contrast filling. No passage into the peritoneal cavity. After 24 hours the contrast medium is collected in sacs with very unhomogeneous appearance.

Operation 27. 11. 1946. On the peritoneum of the uterus and tubes and also on the intestines many nodules were seen. Both tubes were closed, thick, hard and nodular.

Histological examination: The right tube is widened to a sac, filled with blood and amorphous masses. The mucous membrane shows pronounced chronic inflammatory changes and in the stroma there are collections of epitheloid cells similar to tubercles, sometimes with giant cells of Langhans type. In the outer layers of the wall, there are only scattered sparse collections of inflammatory cells. The left tube shows principally the same histological picture. No bacilli were found. In all probability tuberculosis is present.

Judging from these and earlier observations of the author it seems justified to speak of two different forms of roentgenological appearances in tuberculous salpingitis. The first type is characterized by uneven, jagged and ragged contours and small lumen defects. Cases 1 and 7 (fig. 1, 2 and 8) are examples of this type. (Fig. 5, 7, 9, 11, 13, 14 and 15 in the earlier paper.) The anatomical basis for these changes is probably the swollen and tightly folded mucous membrane. The second type is characterized by even, straight or rigid contours and a pipe-like appearance of the tube. Cases 2, 3, 4 and 6 represent this type (fig. 3, 4, 5 and 7 in this and fig. 2, 3 and 10 in the earlier paper). In these cases histological examination shows the folds of the mucous membrane to be very adherent to each other and the lumen looks more or less obliterated. Of course, both types may be seen in the same case. The fistula- and abscess-like processes leading from the lumen may be found in both types. They are probably caused by destruction of tissue in the wall.

In the light of these experiences the author has reexamined the roentgenographic material of the hospital in order to see if the changes found in tuberculous salpingitis are also found in cases with different etiology. Since the earlier results were published about 100 new cases have been added. The last survey therefore is based on about 300 cases of sterility, where at least one tube has been found to be roentgenologically blocked. In the earlier publication 10 cases were described with changes similar to those found in tuberculosis. 17 further cases have now been found with such changes. Of them, 7 have been classified as belonging to the first and 10 to the second type. In the first group no patient

has been operated on, in the second 4. In one of these no biopsy was made. In one of the remaining 3 cases histological examination showed a chronic inflammatory condition without certain evidence of tuberculous origin. In the other 2 cases biopsy showed fibrous tissue formation such as follows healed inflammation and in both, the tubes were filled with putty-like masses. As to the history there was nothing of interest in the first case. One of the remaining patients had had erythema nodosum and the other had been treated for pulmonary tuberculosis. It therefore seems possible, that the salpingitis in these two cases was of tuberculous origin. From the histories in the cases not histologically examined the following facts may be of interest. Of the 7 cases of the first type, one patient had been operated on for appendicitis, 2 patients had suffered from pleurisy and 1 from erythema nodosum. None were reported to have had gonorrhoeal infection or abortion. Of the remaining 7 cases of the second type one patient was operated on for appendicitis and had also been treated for pulmonary tuberculosis, tuberculous peritonitis had been present in one and pulmonary tuberculosis in two more cases. No case was reported to have had gonorrhoeal infection or abortion.

The historical data have of course not much value in determination the etiology in single cases of healed salpingitis, especially as experience shows that gonorrhoeal infection and abortion are often denied where they really have existed. As the material is too little for statistical comparison the author has refrained from comparing the histories in these cases with the other ones.

The frequency of tuberculosis in cases of sterility has been found to be very variable, mostly depending on the different frequencies of gonorrhoeal infection and abortion in different regions. In cases of sterility, operated on for tubal occlusion and histologically examined, MANNHEIMER (8) at Karolinska sjukhuset in Stockholm found tuberculosis in 16 out of 110 cases. In our material of about 320 cases we get the same frequency if we add the suspected to the verified cases, which seems to be good support for the assumption that the diagnosis of tuberculosis in suspected cases is correct in the majority of them. MANNHEIMER has also shown that the absence of histological evidence of tuberculosis does not preclude a tuberculous origin of the salpingitis. (In one patient operated on twice at an interval of 8 years the first biopsy showed typical tuberculosis and the second no signs of it.)

The author has also thoroughly examined the roentgenological appearance in cases, where either a gonorrhoeal infection or a septic infection following abortion had been present. In none of these cases were there pictures similar to those found in tuberculosis, neither could the author find any differences in the appearances as between these two groups.

These findings therefore justify the conclusion, that tuberculous salpingitis in most cases shows a rather typical roentgenological appearance.

Regarding the technique used for HSG in this material the reader is referred to the earlier paper of the author on the same subject, as no change has been made since then. As a contrast medium iodized oil has been almost exclusively used. For the study of the details of tubal anatomy the oil has been found more suitable than the water soluble dyes. As far as the author is aware there have been no instances of a spreading of the tuberculous process in our cases. HSG is of course contraindicated in cases where clinical signs of active inflammation are present, whether tuberculous or otherwise.

From the results of these examinations it is concluded, that with this technique a preoperative diagnosis of tuberculous salpingitis is possible in most cases of sterility, where tuberculosis is the cause. This is of special importance in that curettage in these cases is often negative and perhaps not free from risk, and also preoperative knowledge of the tuberculous origin may influence the indications for operation or at operation the surgical measures to be taken when no macroscopical signs of tuberculosis are present.

The author wishes to express his gratitude to the pathologist at this hospital, Dr. med. F. WAHLGREN and to the gynecologists, Professor B. LUNDQVIST and Docent F. HOLTZ and their assistants for their interest and valuable help in this study.

SUMMARY

In a previous study of the salpingograms in 12 cases of tuberculous salpingitis verified histologically the author found that finely jagged and ragged contours with small lumen defects, and sometimes with abscess- and fistula-like extensions of the tubal lumen, constituted roentgenological signs of tuberculosis. On the basis of further experiences from 7 new cases and from a re-examination of all cases with tubal occlusion a second type of salpingographic picture in tuberculous salpingitis is described, characterized by straight and rigid contours of the lumen and often by a pipe-like configuration of the tube. From the results of these examinations it is concluded that a preoperative diagnosis of tuberculous salpingitis is possible in most cases of sterility, where tuberculosis is the cause.

ZUSAMMENFASSUNG

In einer früheren Arbeit über den hysterosalpingographischen Befund bei 12 Fällen von histologisch bestätigter tuberkulöser Salpingitis hat Verf. gefunden, dass fein gezähnte und ausgefranste Konturen mit kleinen Defekten der Lichtung und manchmal auch abszess- und fistelartigen Ausbuchtungen des Tubenlumens röntgenologische Anzeichen einer Tuberkulose darstellen. An Hand von weiteren Erfahrungen an 7 neuen Fällen und von erneuter Untersuchung sämtlicher Fälle von Tubenverschluss beschreibt

Verf. einen anderen Typus von salpingographischem Befund bei tuberkulöser Salpingitis, der sich durch steife, starre Konturen und eine röhrenförmige Konfiguration der Tube auszeichnet. Aus den Ergebnissen dieser Untersuchungen lässt sich folgern, dass bei der Mehrzahl der durch Tuberkulose verursachten Fälle von Sterilität eine präoperative Diagnose einer Salpingitis möglich ist.

RÉSUMÉ

En étudiant, précédemment, les salpingogrammes de 12 cas de salpingite tuberculeuse vérifiée histologiquement, l'auteur a constaté que des contours finement dentelés et déchiquetés, avec de petites lacunes de la lumière et parfois des prolongements de celle-ci semblables à des abcès ou à des fistules, constituaient des signes radiologiques de tuberculose. Sur la base de l'expérience surajoutée provenant de sept nouveaux cas, et après avoir réexaminé tous ceux avec obstruction de la trompe, il décrit un second type d'image salpingographique dans la salpingite tuberculeuse, qui est caractérisé par des contours rectilignes et rigides de la lumière, et souvent par un aspect en tuyau de la trompe. Le résultat de ces études l'amène à conclure qu'un diagnostic préopératoire de salpingite tuberculeuse est possible dans la plupart des cas de stérilité due à la bacillose.

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FROM THE ROENTGEN-DIAGNOSTIC DEPARTMENT OF THE UNIVERSITY CLINICS IN LUND, SWEDEN (CHIEF: PROF. H. HELLMER)

ROENTGEN EXAMINATION AS AN AID IN THE DIAGNOSIS OF ISLET ADENOMA IN THE PANCREAS[1]

by

Olle Olsson

Islet adenomas originate from the cells in the islands of Langerhans of the pancreas. According to BELL, they are generally small, round tumors with a diameter of 1 to 3 cm., but occasionally they grow to considerable size. They are often situated superficially in the pancreas but may also lie completely embedded in the tissue of the gland. Sometimes they are multiple. Malignant degeneration has been described. The most common situation is the tail of the pancreas, but any part whatsoever of the gland may be involved.

As regards cellular structure, the adenoma belongs to the tumors with endocrine function. Because of its production of insulin, it gives rise to hypoglycemic conditions. Much has been written about the tumor for this reason, both in clinical and pathologic literature. The reason for adding the following case to the numerous ones already described is that here the clinical diagnosis could be established by roentgen examination.

Case report

A woman, aged 32. Medical record 1942/46.

History: — After a few days of headache, abdominal pain and fatigue, the patient was found in bed by a friend, confused but showing no paralysis. She was agitated and talked incoherently. The physician consulted gave scopolamine-morphine whereupon she slept for nine hours. When she awoke she had headache, felt nauseated and vomited. Six hours later she became unconscious and was admitted to the medical hospital.

Examination revealed an ordinarily built, non-obese woman, weighing 57 kg. She was unconscious and lay with wide open eyes and large pupils. The arms and legs were rigid and extended. Profuse perspiration. The breathing was snoring at times. The heart, lungs and abdomen showed nothing abnormal. BABINSKI's sign was positive on both sides.

[1] Submitted for publication, May 9, 1947.

The examining physician, Dr. RADNER, recognized the condition immediately as hypoglycemic coma. The blood sugar measured 0.08 per cent, and thus did not directly belie the clinical diagnosis. The patient was given 30 cc. of a 50 per cent solution of glucose intravenously. Toward the end of the injection, the rigidity began to diminish and the patient regained consciousness. Two minutes after the injection was over the patient was entirely lucid and felt quite well again.

It was obvious that the insulin apparatus was hyperfunctioning and this fact was also borne out by other clinical tests.

With the clinical diagnosis of islet adenoma or cerebral tumor, the patient was referred for roentgen examination.

Roentgen Examination with special reference to the pancreatic bed was made after distention of the stomach with gas according to the Engel-Lysholm method. The distance between the anterior outline of the vertebral bodies and the posterior outline of the stomach in the region of the incisura angularis measured one and one half the width of a vertebral body. Inferiorly in the posterior outline of the corpus ventriculi was an even impression, 2.5 cm. long and 1 cm. deep at the maximum (Fig. 1).

The roentgenographic observations supported the diagnosis of islet adenoma in the pancreas. The patient was transferred to the surgical service.

Operation (Prof. STRÖMBECK). — A reddish blue tumor was found bulging forth on the anterior surface of the pancreatic body six or seven centimeters from the tail in the left edge of the vertebral column. The growth measured about 15 by 15 mm. and showed up distinctly on the otherwise pale pancreas. The involved area of the pancreas bulged forward in an arch, on top of which the tumor was situated. No other tumors were found on inspection and palpation of the pancreas (Fig. 2 a). Excision revealed a round tumor weighing 1.22 gm. (Fig. 2 b).

Microscopic Examination (Dr. LINELL) revealed a growth composed of densely packed cells growing in ramifying columns. Between the columns was a delicate connective tissue stroma containing numerous vessels. Only in one place were the columns seen growing into a few coarse connective tissue fibers containing remains of excretory ducts. The tumor cells were medium and evenly sized and round or polygonal in shape. They had a finely granular protoplasm and fairly small, round nuclei with a fine chromatin network and small nucleoles. They grew mostly in trabecular formations, only occasional tubular structures being seen. The tumor was surrounded by a thin connective capsule, outside which was normal, slightly compressed pancreatic tissue. No cellular polymorphism was seen in the tumor, nor any mitoses. Histologic signs of malignancy were lacking. The diagnosis was *islet adenoma*.

Estimation of Amount of Insulin in the Islet Adenoma (Dr. BORGLIN). — Four hundred mg. of the adenoma were treated according to FISCHER and SCOTT and the insulin in the resulting extract measured according to MARKS, HEMMINGSEN and others. It was found that the preparation contained over $12^1/_2$ but less than 17 I. U. per gram of fresh tissue. Thus it contained between four and five times the amount of insulin in normal pancreatic tissue.

Renewed Roentgen Examination of the pancreatic bed after the operation showed almost complete disappearance of the impression in the posterior outline of the stomach (Fig. 3).

Epicrisis. — After a few days of malaise, a 32-year-old woman became acutely ill. She entered the hospital in a state which the admitting

Fig. 1.

Fig. 3.

Fig. 2 a.

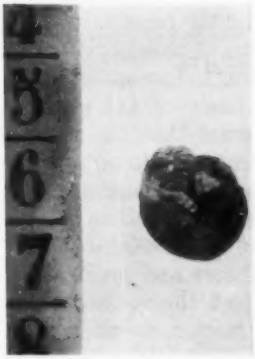

Fig. 2 b.

Fig. 1. Roentgenogram taken according to the Engel-Lysholm method. The stomach is inflated with gas and the picture taken with the rays directed horizontally and the patient in prone position. Thus the straight outline of the gastric cavity anteriorly is due to a fluid level. The posterior outline of the stomach lies one and one half the width of a vertebral body in front of the anterior border of the vertebral bodies. In addition, a local impression is visualized in the area marked with arrows. The site of this impression corresponds to that of the islet adenoma found at operation.

Fig. 2 a. Photograph of the islet adenoma during operation.

Fig. 2 b. Photograph of the excised islet adenoma. Weight 1.22 gm.

Fig. 3. Roentgenogram of the stomach after operation, taken in the same way as the film shown in figure 1. The local indentation in the posterior stomach wall has disappeared.

physician immediately recognized as hypoglycemic coma in spite of the normal blood sugar level. On receiving glucose the patient recovered instantaneously. As she had not taken any insulin, islet adenoma was suspected. Roentgen examination according to ENGEL and LYSHOLM revealed a local indentation in the posterior wall of the gas-filled stomach. Operation disclosed a small, well defined pancreatic tumor at the site of the indentation. The tumor had the microscopic structure of islet adenoma. Roentgenograms taken after removal of the tumor showed the impression in the posterior outline of the stomach to have disappeared.

The possibilities of diagnosing pancreatic lesions roentgenographically are extremely limited. Apart from the rare cases of pancreatic stones and gas in abscesses, the roentgenologic signs of pancreatic disease are indirect. In chronic cases, one is mainly referred to changes in the stomach and duodenum. The ENGEL-LYSHOLM technic has proved to be good for demonstrating changes in the size of the pancreas due to cancer.

Method. — The stomach is filled with gas by having the patient take an ordinary effervescing powder. Pictures are then taken with the rays directed horizontally in the prone and supine position and one in the supine position in the anteroposterior direction. The region between the posterior wall of the stomach and the anterior border of the vertebral column is occupied by the pancreatic bed. When the pancreas is enlarged, this distance is increased. The distance is abnormal whenever it exceeds the width of one vertebral body.

The relativity of the measurement naturally makes the method slightly uncertain. The first report on this form of diagnosis drew attention to this unreliability, especially in the case of obese patients. In 1941, HOLM, LYSHOLM's pupil, attempted to set the limits for the normal on a basis of 449 examinations of the pancreas by this method. He concluded that the method must be considered an examination of the pancreatic bed, not of the pancreas itself. He made this reservation after noting an increase in the distance between the spine and the posterior stomach wall in a number of conditions which did not directly involve the pancreas, *e. g.*, retroperitoneal tumors of different kinds, hepatic tumors and ascites. Furthermore, the physical build of the patient may affect the measurements. In the present case, the distance between the posterior stomach wall and the anterior outline of the vertebral bodies was one and one half the width of a vertebral body.

According to HOLM's research, this distance, while it excites suspicion, is not definitely abnormal. However, there was also a local indentation in the posterior stomach wall, 2.5 cm. long and 1 cm. deep at the maximum, pointing to an expanding lesion in a circumscribed part of the pancreatic bed. Operation revealed that the pancreas had the shape of an arch, on the tip of which an islet adenoma was situated. The tumor lay at the site of the impression in the posterior stomach wall in the

roentgenogram. It is, therefore, highly probable that the impression was caused by the islet adenoma.

In their original paper on this subject, ENGEL and LYSHOLM pointed out that pancreatic cancer was not only manifested in an increased distance between the spine and the posterior stomach wall. The method they advocated also permitted »the demonstration of local depressions into the inflated stomach, indicating localised tumor formation of smaller size». As they said: »Observations of this nature will of course render more reliable the estimation of the changes as pathological and will yield important information regarding their nature.» Thus the local change, as experience has shown, is the most reliable sign of abnormality. Even small tumors in the pancreas may be diagnosed roentgenographically through the demonstration of local changes. The observation of ENGEL and LYSHOLM just quoted refers to pancreatic cancer but it also applies to benign tumors in the pancreas. Islet adenoma is the most important of these tumors from a practical standpoint. If the adenoma is situated anteriorly in the pancreas and in the body or tail, the clinical diagnosis may be substantiated, as the present case shows, by the demonstration with the Engel-Lysholm method of a local expanding lesion in the pancreatic bed. The demonstration of a lesion of this kind also points strongly to the advisability of surgical intervention.

SUMMARY

Whenever islet adenoma in the pancreas is suspected, the pancreatic bed should be examined roentgenographically according to the ENGEL-LYSHOLM method. The demonstration of a local expanding lesion in this bed bears out the clinical suspicions and act as a guide to surgical treatment.

ZUSAMMENFASSUNG

Wenn Verdacht auf Inseladenom des Pankreas besteht, kann das Pankreasbett nach der Engel-Lysholm'schen Methode röntgenologisch untersucht werden. Der Nachweis eines lokal expansiven Prozesses in diesem Bette bestätigt den klinischen Verdacht und dient als Leitfaden für die chirurgische Behandlung.

RÉSUMÉ

Chaque fois qu'on soupçonne un adénome insulaire du pancréas on devrait examiner radiologiquement le lit de la glande, selon la méthode D'ENGEL-LYSHOLM. La mise en évidence d'une lésion locale qui s'étale dans ce lit confirme les suspicions cliniques et sert de guide au traitement chirurgical.

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FROM THE NEUROROENTGENDIAGNOSTIC LABORATORY (HEAD: OLLE OLSSON, M. D.) AND THE NEUROSURGICAL DEPARTMENT (HEAD: LARS LEKSELL, M. D.) OF THE UNIVERSITY CLINIC OF LUND, SWEDEN.

INTRACRANIAL ANGIOGRAPHY VIA THE VERTEBRAL ARTERY[1]

Preliminary report of a new technique

by

Stig Radner

Cerebral angiography after the injection of radiopaque substance into the internal carotid is now generally accepted as a valuable and safe method for investigating intracranial lesions. By this method the carotid system of the cerebrovascular tree is visualized; the posterior cerebral artery is occasionally seen but other vessels of the vertebral system are hardly ever disclosed in these angiograms.

This means that carotid angiography is of no practical value when it comes to visualizing the vertebral system supplying nervous structures in the middle and posterior cranial fossa. Several methods have been proposed to bring into relief also this vascular system.

Previous Methods

Moniz (1934) exposed the subclavian artery, which he strangulated peripherally and then injected into it thorotrast. By this means he was able to obtain angiograms of the arterial branches in this region including the intracranial vertebral system.

Later Shimidzu (1937) applied a similar technique; after compressing the axillary artery, he injected thorotrast percutaneously into the subclavian artery.

Also Sjöquist (1938) tried to use the technique adopted by Moniz, but he found it inadequate and introduced a new method. After exposure of the vertebral artery, he injected thorotrast direct into same and produced good angiograms in six cases out of eight.

Elvidge (1938) obtained angiograms of the basilar circulation by means of the counter-current injection of opaque material into the com-

[1] Submitted for publication, June 7, 1947.

Fig. 1. The catheter is introduced via the right radial artery and the subclavian into the vertebral artery.

mon carotid artery. During injection this artery was compressed distally and also the axillary artery was occluded by pressure.

TAKAHASHI (1940) radiographed the vertebral system after percutaneous puncture and direct injection of thorotrast into the vertebral artery.

BERCZELLER and KUGLER (1937) made angiograms in preparations after exposing the vertebral artery at the Atlas and subsequent direct injection. It would seem, however, that these authors have not published any results obtained when practising their method on living human beings.

A diagnostic method must be fairly safe, conclusive and easy, but none of the above processes appear to satisfy these requirements, nor have any of them been generally adopted for routine examinations. We are, however, in need of such a method to visualize the vertebral vascular arrangement and thus fill the diagnostic void behind the carotid system of the brain.

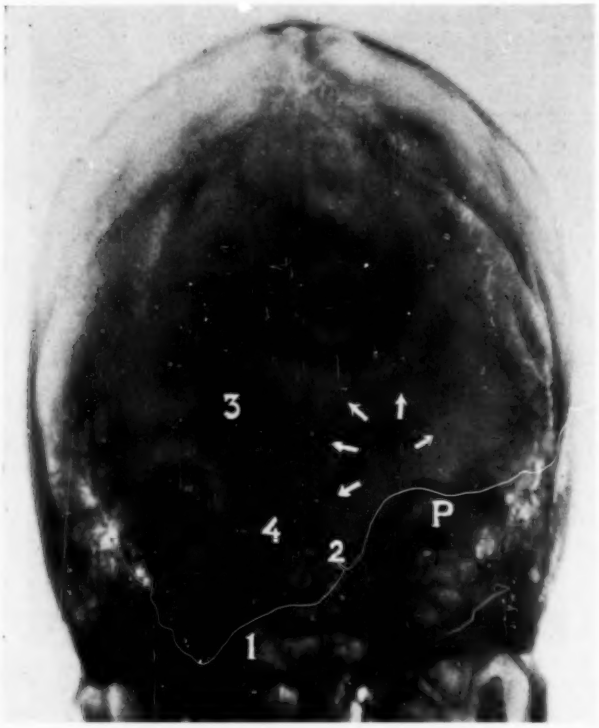

Fig. 2. Angiogram of the vertebral vascular system. The picture is taken after the injection of 10 ml. diodrast through the catheter. — 1. Vertebral artery. — 2. Basilar artery. — 3. Posterior cerebral artery and superior cerebellar artery. — 4. Inferior posterior cerebellar artery, visualized only on the side of the injection. — P. Left Porus acust. intern.; dilated. — The arrows indicate a curved displacement of the superficial cerebellar vessels around the Porus; these vessels are concentrically arranged. The displacement is caused by a walnut-sized acoustic tumor. — Verification through operation.

The Author's Method

During an anatomical investigation with another purpose in view[1] the author accidentally discovered that the vertebral artery of a prepa-

[1] The author is working on the angiography of the coronary blood vessels; after catheterization of the aortic bulb via the radial artery, diodrast is injected through the catheter. The results of these investigations will be published later. By means of this method it may also be possible to reveal pathological conditions of the aorta, *e. g.* coarctation of aorta, patent ductus arteriosus, etc.

ation may be catheterized via the radial artery. Later, whilst working at the Neurosurgical Department, he was able to show that also the vertebral artery of living beings may be catheterized in the same manner. After the injection of radiopaque substance through the catheter, angiograms of the vertebral system may be obtained.

After local anesthesia, the radial artery is exposed roughly between the middle and the distal third of the forearm. The incision in the skin may be about 1 cm. long. The artery is ligated distally in the wound, whilst a tourniquet is applied proximally therein. A small cut is made in the isolated part of the vessel into which is inserted an ordinary urethral catheter. The tourniquet is then removed and the catheter is introduced further by gentle pressure and under fluoroscopic control. When the catheter has entered the vertebral artery, 10 ml. diodrast of 35 per cent conc. is injected, whereafter angiograms are taken in suitable projections.

When the catheter is removed, the radial artery is ligated also proximally of the cut in the vessel. Thanks to the abundant collateral circulation in this region there will be no palpable difference in the radial pulse after ligation.

This method, hitherto adopted in but a few cases, must be tested more. The wider use of it is intended, and the experience obtained on a more extensive material will be published later.

SUMMARY

After a survey of previous methods to visualize the intracranial part of the vertebral vascular system, the author describes a new method. The vertebral artery is catheterized via the radial artery and radiopaque substance is injected through the catheter.

ZUSAMMENFASSUNG

Nach einer Übersicht der bisherigen Methoden zur Sichtbarmachung des intrakranialen Teiles des vertebralen Gefässystems, beschreibt Verf. eine neue Methode. Die Art. vertebralis wird von der Art. radialis aus kathetrisiert und durch den Katheter radioopake Substanz eingespritzt.

RÉSUMÉ

Après une revue des anciennes méthodes servant à mettre en évidence la partie intra-cranienne du système vasculaire de l'artère vertébrale l'auteur en décrit une nouvelle. L'artère vertébrale est cathétérisée à partir de l'artère radiale et une substance opaque aux Rayons Roentgen est injectée par la sonde.

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FROM ALTA BATES HOSPITAL, BERKELEY, CALIF., U. S. A.

FIRST INFECTION PULMONARY TUBERCULOSIS IN THE YOUNG ADULT[1]

by

Henry B, Zwerling, M. D.

In pulmonary tuberculosis the parenchymal lesion without adenopathy is usually considered evidence of reinfection disease only, and yet it is known that by roentgenographic means alone it is difficult, if not impossible, to differentiate between first infection and reinfection in the young adult. (1) The history of proven healed first infection or of a positive tuberculin reaction in the past justifies the diagnosis of reinfection tuberculosis in the presence of a new lesion, but it is not often that these criteria are fulfilled. More frequently, the first knowledge of tuberculosis is the roentgenographic demonstration of a lesion in an individual with no previous history of tuberculous disease or of tuberculin skin reaction.

To justify the diagnosis of reinfection tuberculosis on the basis that most urban dwellers are sensitive to tuberculin by early adult life, is no longer tenable (1). It is probable that the large test doses of tuberculin used in the past, and even today, provoked many non-specific skin reactions (2) which were erroneously considered an indication of previous tuberculous infection. Further, PALMER in his study of student nurses (3) has demonstrated that in many schools of nursing in the United States less than fifty percent show a positive reaction to tuberculin by the third year in training. Since the degree of exposure to active tuberculosis is considerably greater among student nurses than in the general population of a similar age group (18—21 years), it is probable that a large segment of the young adult population has never had first infection tuberculosis.

Another argument advanced in favor of the diagnosis of reinfection, rather than first infection, is the demonstration of active tuberculosis in the presence of pulmonary calcification. It is now evident that pul-

[1] Submitted for publication, Jan. 10, 1947.

monary calcification in the United States is not necessarily related to sensitivity to tuberculin and therefore, to previous tuberculous infection (4, 5). Pulmonary calcification is frequently associated with sensitivity to histoplasmin and to coccidioidin, and can be no longer considered incontrovertible proof of tuberculous infection. Up to the present time there is no certain method of differentiating between calcification associated with tuberculin or histoplasmin sensitivity.

It is generally accepted that first infection tuberculosis is associated with involvement of regional lymph nodes. It is not generally realized, however, that roentgenographic demonstration of lymphadenopathy is not always possible, especially if the disease causes little or no enlargement of the nodes. A parenchymal focus is usually readily demonstrable because it is seen against a background of air-containing lung, whereas hilar lymph nodes must be markedly enlarged to be appreciated against the background of mediastinal structures, unless special techniques are used.[1] If the lymphadenopathy is not roentgenologically apparent, the diagnosis of reinfection tuberculosis is based on the perception of a parenchymal focus which may be a first infection lesion.

In the student nurse study being conducted by PALMER, the diagnosis of first infection tuberculosis was based on the appearance of a lesion after a negative roentgenogram of the chest, associated with conversion of the tuberculin reaction from negative to positive. A preliminary analysis indicates that parenchymal foci without demonstrable adenopathy are at least twice as common as those instances with demonstrable adenopathy. These parenchymal lesions cannot be distinguished roentgenologically from the so-called reinfection minimal.

It has occasionally been stated that lymph node response to infection is a function of age: The younger the individual, the more marked the enlargement of the involved nodes. HIGH and ZWERLING (6), in a study of almost two hundred instances of tuberculosis among American Indian children ranging in age from 1—20 years, demonstrated lymph node enlargement far more commonly in the younger age groups. The older the individual was at the time of the first infection the less the likelihood of adenopathy being roentgenologically apparent. This supplements the finding of so-called minimal first infection lesions in the student nurse study, in that the student nurse group has a more limited age range.

Comment

Several points have been presented to suggest that much of the pulmonary tuberculosis in the young adult is of the first infection type.

[1] In the study of student nurses and of Indian children only postero-anterior films of the chest were made.

Whether first infection is more or less common clinically than reinfection in the age group up to 20—25 years or beyond, cannot be stated at this time. It is probable that a significant number of instances of »minimal» pulmonary tuberculosis in the young adult and possibly in older age groups are first infections.

The importance of distinguishing first infection and reinfection in the early small lesion is academic at this time, since it is apparent that in either instance the disease may become progressive. It is possible, however, that complete recovery from a first infection may be associated with increased resistance, such as is afforded with BCG vaccination. If recovery from first infection is comparable to BCG vaccination, an arbitrary danger period of two years should be postulated to allow for exacerbation, and to permit resistance to increase to a sufficiently high level as was demonstrated by ARONSON and PALMER (7) in their recent study of the effect of BCG vaccination. The latter study indicated a significant degree of immunity was attained two and more years after vaccination.

It is not intended that the foregoing be accepted without reservations as the existence of reinfection and endogenous exacerbation in tuberculosis is not denied. The probability is presented that first infection pulmonary tuberculosis is frequently erroneously considered reinfection in the young adult, and possibly in the older age groups as well.

SUMMARY

Clinical pulmonary tuberculosis in the young adult is frequently of the first infection type. Recovery from a primary infection probably results in immunity similar to that afforded with B. C. G.

ZUSAMMENFASSUNG

Klinische Lungentuberkulose bei jugendlichen Erwachsenen gehört oft dem primären Infektionstypus. Heilung nach einer Primärinfektion gibt wahrscheinlich eine Immunität, wie nach B. C. G-Impfung.

RÉSUMÉ

La tuberculose pulmonaire clinique de l'adulte jeune est fréquemment une infection de la type d'une infection primaire. La guérison d'une infection primaire aboutit probablement à une immunité semblable à celle que procure le B. C. G.

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FROM THE DEPARTMENT OF RADIOLOGY, TEMPLE UNIVERSITY SCHOOL OF MEDICINE, PHILADELPHIA, U. S. A.

ROENTGEN ELEKTROKYMOGRAPHY [1]

by

W. Edward Chamberlain

Roentgenology has established itself as a major contributor in the fields of normal and morbid *anatomy*. That its contribution to normal and morbid *physiology* has been somewhat less is due largely to two factors; (a) the inherent limitations of fluoroscopy (1), and (b) the lack of a satisfactory cinematographic method.

A step in the direction of a greater degree of integration of roentgenology into physiology is reported in this paper. The apparatus here described is practical and universally available. When used in conjunction with any ordinary clinical fluoroscope, it will produce graphic records of such physiologic processes as the pumping action of the heart and the systolic-diastolic filling and emptying of the aorta or pulmonary artery. When properly oriented it will even record such »invisible» phenomena as the cyclic filling and emptying of the lung vessels out in the parenchymal zones of the lung fields or the changes in »thickness» (dorsoventral dimension) of the heart that accompany the cardiac cycle.

History. — Roentgen kymography (2, 3, 4, 5, 6, 7, 8, 9) is the oldest and most used method of recording the cyclic movements of the borders of the heart-vessel shadow. Records of this type were reported by SABAT as early as 1911. The method achieved notable success in the hands of STUMPF and HIRSCH.

In 1925 the author with W. DOCK (10, 11), produced graphic records of heart motion by measuring successive frames of a cinematographic sequence made with the roentgen cinematograph of RUGGLES. At that time we proposed to devise an »electrokymographic» method utilizing (1) the fluoroscope, (2) an ionization chamber back of an aperture or slit in a shield of metallic lead, (3) a suitable electronic amplifier and (4) a recording galvanometer. In 1942 G. C. HENNY and R. TAFT, collaborating with the author, produced records of heart-border motion with a system

[1] Submitted for publication, July 3, 1947.

of this type. But the obstacles to producing a stable »D. C.» amplifier with extremely high gain proved rather formidable and the effort was temporarily abandoned.

In 1937 HECKMANN (12) reported the use of a photo-electric cell with amplifier and recording galvanometer to record the changes in roentgen ray transmission that occur at the heart as a result of systolic-diastolic changes in its dorso-ventral dimension. Quite recently MARCHAL (13) described a somewhat similar device.

The advent of the »multiplier phototube», and its successful application by MORGAN and HODGES (14) to the measurement of the intensity of an efferent roentgen beam and the automatic termination of the roentgenographic exposure, offered a new approach. In 1944 G. C. HENNY and B. R. BOONE, working in the author's department, and following a direct suggestion by R. H. MORGAN, produced a practical instrument and records that left little to be desired in the way of fidelity and good detail (15). In the three years that have passed since our initial success, minor improvements have evolved but fundamental changes have seemed neither necessary nor advisable (16).

Special mention should be made of the work of G. HJELMARE, E. LYSHOLM and co-workers, begun in 1937 with photo-electric cells and amplifiers, and further developed with GEIGER-MÜLLER counter tubes and special amplifiers, as reported in 1946 (17). Had the multiplier phototube (Radio Corporation of America) been available to these investigators, roentgen electrokymography would doubtless have become practicable many years ago.

Apparatus. — Essentially the apparatus for electrokymography consists of the clinical fluoroscope, the »pick-up» with its power supply, filter, etc., the recording galvanometer (any good electrocardiograph) and some way of recording simultaneously, as a time-reference curve, an arterial pulse tracing, a stethogram (heart-sound record) or an electrocardiogram.

Any clinical fluoroscope may be used. The current and voltage settings that are ordinarily used for clinical fluoroscopy have been found

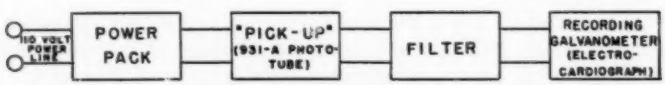

Fig. 1. Diagram to show relationship of essential parts of the electrokymograph. Usually the »power back» (fig. 3) and »filter» (fig. 2) are housed together in a suitable carrying case (1, fig. 4, left). The »pick-up» is mounted on screen of fluoroscope (2, fig. 4, left). Its position in relation to heart shadow is controlled fluoroscopically. Without the »filter» the tracings produced by the recording galvanometer would be unreadable, due to registration of the rapid alternating-current fluctuations (»ripple») in the fluoroscopic roentgen beam.

entirely adequate for electrokymography. We customarily use 2 ma to 3 ma at 85 kv peak. Self rectified operation of the roentgen tube is possible, but definite advantage is gained from full-wave, 4-valve rectification when such is available. This is because it is easier to filter out the »ripple» in the roentgen beam at 120 pulses per second (60-cycle A. C., full-wave-rectified) or 100 pulses per second (50-cycle A. C., full-wave-rectified) than it is at 60 or 50 pulses per second (60-cycle or 50-cycle A. C., half-wave-rectified or self-rectified). This filtering out of the ripple in the roentgen beam is an essential part of electrokymography because without it the galvanometer follows these rapid fluctuations in the output of the roentgen tube and the record produced by the galvanometer becomes blurred.

There are two principal reasons for the fact that it is easier to filter out a 120-pulse or 100-pulse ripple than one of 60 or 50 pulses per second. (1) In the case of full-wave rectification, if the roentgen tube is of the cable-connected, »shock-proof» type, the capacitance of the insulated and shielded cables will suppress a high percentage of the voltage fluctuation at the terminals of the roentgen tube. This is particularly true at customary fluoroscopic settings of 2 to 3 milliamperes. (2) The cardiodynamic phenomena which we are recording exhibit frequencies of the order of 1 to 25 cycles per second. In order to record these phenomena with complete fidelity, it is necessary that the filter give zero transmission at the unwanted frequency of the ripple in the roentgen beam, and no selective absorption at the frequencies of the physiologic processes. It is easier to achieve this for a 120-pulse or 100-pulse ripple than it is for a 60-pulse or 50-pulse ripple, the latter being much closer to the maximum frequencies that may be encountered in these physiologic processes.

The filters shown in figure 2 are for 60-cycle alternating current, 120-pulse or 60-pulse ripples. We have had no experience with 50-cycle alternating current. Therefore we are not able to stipulate the exact values for the resistances and capacitances (R_{13} to R_{20}, C_2 to C_{10}, figure 2) for filtering out the 100-pulse or 50-pulse ripples that would be present with 50-cycle current. We can, however, indicate the way in which these values may be determined. These filters are Wien bridges in slightly altered form, and formulae for »zero transmission» at stipulated frequencies are given on pages 905 and 918, TERMAN's »Radio Engineers' Handbook», McGraw-Hill Book Company, New York and London, 1943.

The electrokymographic pick-up (see 2, figure 4, left) consists of the multiplier phototube with its voltage-divider resistance network (see R_1 to R_{10}, figure 2), enclosed in a special housing. A metallic lead diaphragm with aperture 5 mm by 20 mm gives appropriate dimensions to the effective portion of the roentgen beam. A piece of fluorescent screen is closely applied to the phototube, with its active surface facing the sensitive area

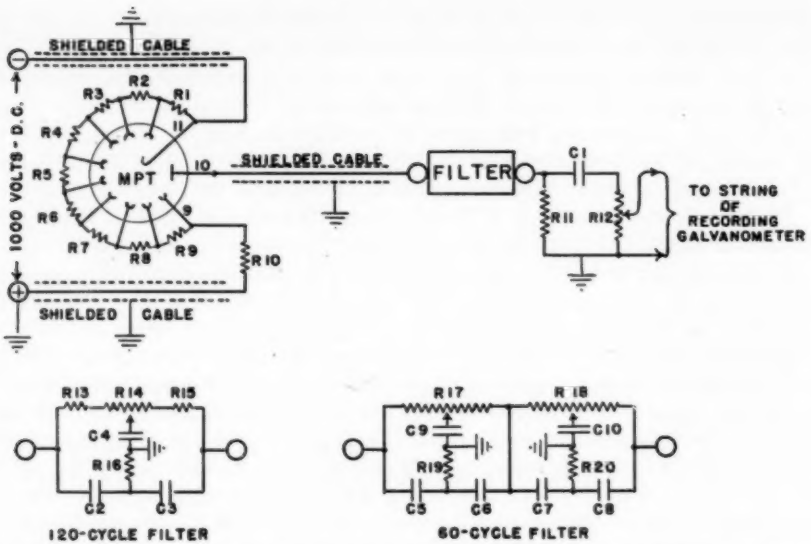

Fig. 2. Wiring diagram of electrokymographic »pick-up» and two types of filter. MPT = = RCA (Radio Corp. of Amer.) 931-A (or 1 P 21) multiplier phototube. R_1 to $R_9 = 0.1$ megohm, half-watt resistors. $R_{10} = 50{,}000$ ohms, half-watt. $R_{11} = 1$ megohm, half-watt $R_{12} = 10{,}000$-ohm potentiometer (carbon), linear taper. R_{13} and $R_{15} = 10{,}000$ ohms, half-watt. $R_{14} = 20{,}000$-ohm potentiometer (carbon). $R_{16} = 17{,}500$ ohms, quarter-watt. R_{17} and $R_{18} = 100{,}000$-ohm potentiometers (carbon), linear taper. R_{19} and $R_{20} = 7{,}000$ ohms, quarter-watt. $C_1 = 2$ mfd paper condenser. C_2 and $C_3 = 0.05$ mfd paper. $C_4 = 0.18$ mfd paper. C_5, C_6, C_7 and $C_8 = 0.1$ mfd, 400-volt, paper. C_9 and $C_{10} = 0.06$ mfd, 400-volt, paper. (For alternative values of C_1, R_{11} and R_{12}, see text.)

of the phototube cathode. We have used Patterson Type B screen and a special Patterson, Q 29—774 C, more or less interchangeably. The latter is an experimental screen which emits light of a color particularly suited to the spectral sensitivity of the phototube. We believe that any fluorescent screen which is sufficiently free from lag may be used for this purpose.

The above-described »pick-up» is light in weight and of small size. It is mounted at the center of the regular fluoroscopic screen so that when the shutters are closed to produce a narrow roentgen beam, the 5 mm by 20 mm aperture of the phototube housing is readily aligned with a selected part of the patient's heart shadow (or lung field).

The »power pack» shown in figure 3 is just one of many circuits that might be used for this purpose. Any adequately filtered »battery eliminator» will serve the purpose. Obviously one could use a series of radio »B-batteries».

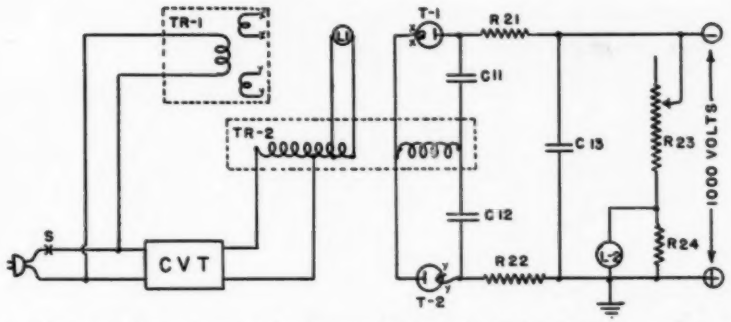

Fig. 3. Diagram of a »power pack» for production of 1,000-volt D. C. supply for the electrokymograph. S = power control switch. CVT = »Sola» constant voltage (»stabilizer») transformer, 301,003, 15 watt. TR_1 = SNC (SNC Manufacturing Co., Glenview, Illinois) 4 P 222 dual filament, 2.5-volt transformer. TR_2 = SNC 8 P 186 power transformer, 325—0—325 volts. L_1 = 6-volt pilot lamp (of low candle power). L_2 = G. E. three-quarter watt, 125-volt, neon lamp. T_1 and T_2 = 2 × 2 (879) rectifier tubes. R_{21} = 0.2 megohm, 2-watt resistor. R_{22} = 0.1 megohm, 2-watt. R_{23} may be a 2-watt resistor of approximately 1.7 megohms, variable type, adjusted to give output of 1,000 volts to phototube network. (A potentiometer of corresponding type may be substituted for R_{23}.) R_{24} = 150,000 ohms, 2-watt.

In figures 2 and 3 we have specified 1000 volts as the D. C. supply. Lower voltages may prove adequate. If the recorder (electrocardiograph) is of the amplifier-galvanometer type, the weakening of the signal due to this lowered voltage may readily be compensated for simply by turning up the gain control of the amplifier. B. R. Boone, Senior Surgeon, U. S. Public Health Service, working in the author's department, is experimenting with a simplified, 700-volt power pack, using one stage of audio-frequency amplification just ahead of a string galvanometer. Such an arrangement may turn out to have definite advantages.

Boone is also investigating variations in the arrangement for coupling the phototube output with the galvanometer (or amplifier). The blocking condenser (C_1 of figure 2) is essential. Without it the galvanometer would record the D. C. component of the signal instead of only the significant fluctuations. But the resistances, R_{11} and R_{12}, must have correct values for the required »time constant». If this time constant is too long, valuable time will be lost at the beginning of each record because the suppression of the D. C. component of the signal will take place too slowly. On the other hand, if the time constant is too short, fidelity will be lost. (*E. g.*, horizontal segments in the electrokymogram will be reproduced as slopes toward the base line.)

In the caption for figure 2 we have specified: C_1 = 2 mfd, paper; R_{11} = 1 megohm, half-watt; R_{12} = 10,000 ohm potentiometer (carbon),

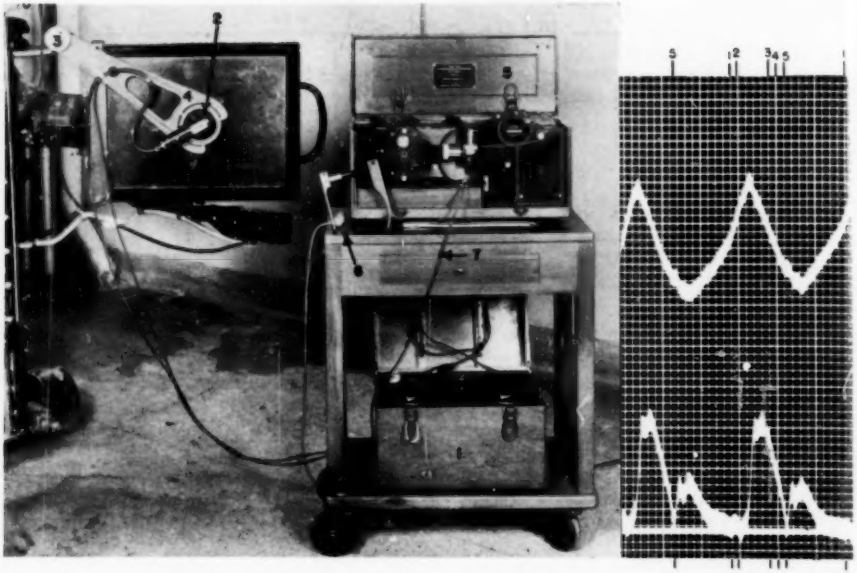

Fig. 4 (left). Electrokymograph with »pick-up» mounted at center of fluoroscopic screen. 1 carrying case containing »power pack», »filter», etc. 2 »pick-up» housing which encloses multiplier phototube, metallic lead diaphragm with 5 mm by 20 mm aperture (visible in photograph), small piece of fluorescent screen and resistance divider network (R_1 to R_{10} of fig. 2). 3 pulley for belt drive which permits operator to rotate »pick-up» without approaching roentgen beam. 4 arm, of plywood or plastic. 5 electrocardiograph (recording galvanometer). 6, 7 »cup» of carotid pulse neckpiece, and rubber tubing for conducting pulse wave to recorder.

Fig. 4 (right). Upper curve is a graph of changing density, an electrokymogram made with pick-up directly over shadow of left ventricle instead of at shadow border. It traces fluctuations in dorso-ventral dimension. Lower curve is of carotid pulse. Vertical time lines show intervals of 0.04 second. Note that density (thickness) continues to increase rapidly during »isometric contraction» and for 0.06 second after onset of systolic ejection. For significance of code numbers in identifying cardiodynamic events, see caption of fig. 5.

linear taper. BOONE has recently found that there are apparent advantages in some very different values. C_1 may be given a value of 10 mfd, in which case a paper condenser becomes inconveniently bulky and an electrolytic condenser may be substituted. A satisfactory electrolytic condenser of 10 mfd capacitance gave a bias of »50 volts, working», and was connected with its positive pole toward R_{11}, negative toward R_{12}. The value of R_{11} must now be changed. One hundred thousand ohms has proven satisfactory but a variable resistor might be better since there is

some reason for believing that a value for R_{11} as low as 50,000 ohms may prove advantageous.

It should be emphasized that any satisfactory electrocardiograph may be used as the recording galvanometer for electrokymography. We have had equal success with one that uses an Einthoven string galvanometer (Cambridge Instrument Company's »Simplitrol») and one with a mirror and light beam galvanometer of the D'Arsonval type, fed from a power amplifier (the Sanborn »Cardiette»). To a certain extent the two types are completely interchangeable, since it is a simple matter to substitute one for the other in any of the circuits we have worked with. It may be, however, that each of these types of recorder will require a particular type of coupling circuit for optimum results.

For identification of the various phases of heart action we have used simultaneously recorded heart sounds, electrocardiograms and carotid pulse tracings. Of these we have found the carotid pulse tracing most advantageous, for it bears a constant relationship to certain important phases of the pumping action of the left ventricle. The various landmarks on the electrocardiogram do not maintain such a constant relationship. It is easy to show that on the time axis of the dynamic heart cycle, the EKG waves may shift forward or backward in such a way as to make them less reliable than the pulse tracing, as timers for identification of the phenomena revealed by the electrokymogram.

In the beginning we assumed that multiple-beam recording (*e. g.*, simultaneous records of aortic arch and pulmonary artery, or of left ventricular border and ascending aorta, etc.) would be very desirable if not essential. Through the courtesy of the Cambridge Instrument Company, makers of the »Simplitrol» electrocardiograph which we have used extensively in our work, we were able to obtain experience with simultaneous recordings (on 12 cm wide paper instead of the usual 6 cm width) of three galvanometer string shadows, one to three pulse tracings and one heart sound track. This elaborate device has been extremely useful as a research instrument in the laboratory of physiology. But for work in the clinical fluoroscopic room we have come to prefer a single electrokymographic tracing plus a simultaneous tracing of the carotid pulse for timing the observed events. We have found much satisfaction in producing simultaneous records of heart sounds (see figure 5) but we have not been able to convince ourselves that the »phonocardiogram» (or »stethogram») is completely interchangeable with the carotid pulse tracing as a time-reference curve for electrokymography.

As a result of our emphasis upon the carotid pulse tracing, we became dissatisfied with the pulse recorder that is ordinarily supplied with an electrocardiograph. The perfected pulse recorder devised by BOONE and HENNY has been described in considerable detail (16). The carotid pulse

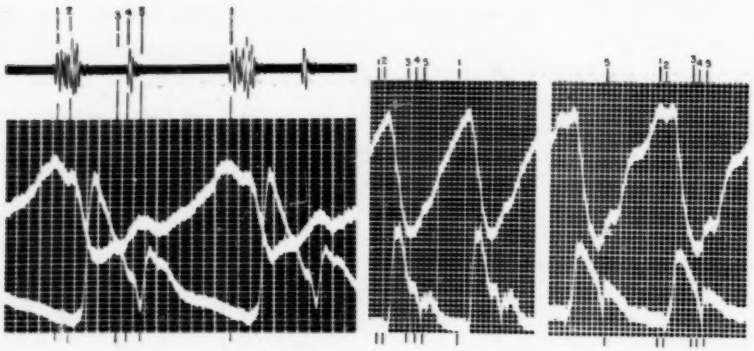

Fig. 5. Sample electrokymograms from left ventricles in three normal subjects. In each case the lower tracing is of carotid pulse. Record on left shows simultaneously recorded heart sounds, with registration at 50 mm per second. The other records were made at standard speed of 25 mm per second. In both types of record the vertical time lines are at intervals of 0.04 second.

Based upon accepted interpretations of carotid pulse tracings and accepted values for pulse-transmission times, the indicated points of phase change, numbered 1 to 5, have the following significance. 1—2, isometric contraction; 2—3, systolic ejection; 3—4, protodiastole; 4—5, isometric relaxation; 5—1, diastolic filling.

tracings reproduced in this paper were all made with this improved pulse recorder, except in the case of figure 6 E, which was obtained at an earlier date.

Records and Interpretation (18). — The significance of various landmarks on the carotid pulse tracing has been well established in the physiology laboratory. Our interpretations of the electrokymograms that are reproduced in this paper, are based upon these known facts. In the code we have adopted, 1 marks the time of closing of the mitral valve; 2, the time of opening of the aortic valve; 3, the onset of protodiastole; 4, the time of closing of the aortic valve; 5, the time of opening of the mitral valve. From this it follows that the interval 1—2 represents the phase of »isometric contraction»; 2—3 is occupied by systolic ejection; 3—4 represents the phase of »protodiastole»; 4—5 comprises »isometric relaxation»; 5—1 represents diastolic filling of the ventricle.

For correct interpretation of the electrokymogram due allowance must be made for pulse-wave-transmission delays and for a constant lag of exactly 0.01 second in the carotid pulse tracing due to transmission time in the air-conduction tubing (7, figure 4, left). When this is done, it is frequently possible to identify many of the above-numbered events of the cycle, on tracings from the left heart border (left ventricle). For example, in the third tracing of figure 5, the sharp changes of direction of

order motion at points coded 1 and 2 are approximately 0.05 second ahead of their corresponding points on the carotid pulse tracing. This is well within the limits of normal variation for the time delays involved in this relationship.

Ventricular tracings are apt to show »positional changes» at the beginning and end of systole, due to a change of shape, the heart being more spherical during systole and more elongated or pear-shaped during diastole. These »positional changes» may occur in either direction. That is, they may result in an increased amplitude or a decreased amplitude of the true »volume-change» motion, or they may even produce a reversal of the expected direction of a border motion. For example, in the left ventricular tracing of figure 4 (right), the beginning of isometric contraction is characterized by an increase in *outward* motion, due to a shape change toward the spherical; and this relatively rapid *outward* motion continues on into the phase of systolic ejection for almost 0.06 second. This particular record was made with the pick-up directly over the ventricle instead of at the shadow border. It is therefore a graph of changing thickness (or dorso-ventral dimension). It would therefore be more accurate to state that the increase in thickness which is ordinarily a feature of diastole, is seen to continue on for 0.06 second into the phase of systolic ejection. Correspondingly, the decrease in thickness that is ordinarily a feature of systolic ejection, is seen to continue on (after a very brief »check» at the moment of opening of mitral valve) for the initial 0.09 second of early diastole.

Electrokymograms of the pulmonary artery, at or very near its origin, are extremely easy to obtain (figure 6 A, C, D). In a series of 100 normals we have investigated the degree of asynchronism of ejection of the right and left ventricles by electrokymography of the pulmonary artery, the ascending aorta, the aortic knob and the ventricular walls (19). We found the »PAC interval» (the interval between the »take-off» of the ejection limb of the pulmonary artery tracing and the corresponding point on the carotid pulse record) to vary between + 0.03 second and — 0.01 second. In other words, the pulmonary artery pulse wave may appear as much as 0.03 second ahead of the carotid wave, or as much as 0.01 second behind same. In all but one of a series of 12 cases of bundle-branch block the PAc interval was outside normal limits (see figures 6C and 6D). In that one case (clinically a case of left bundle-branch block) the PAc interval was + 0.03 second, at the limit of normal variation.

In cases of myocardial infarction (figure 6 E) our data substantiate those obtained with the roentgen kymograph, and many of our tracings show a remarkable resemblance to the graphs obtained in the dog, by Fenant and Wiggers (20), through the application of clamps to the coronary arteries. During systolic ejection the usual inward motion of the

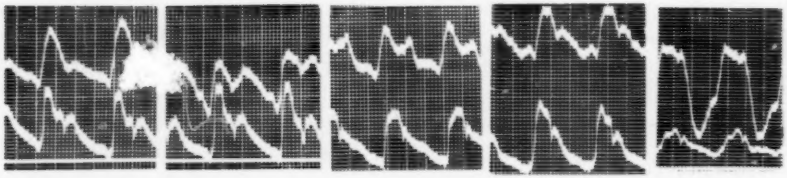

Fig. 6. Sample electrokymograms. In each record the lower tracing is of carotid pulse. Due to transmission time in air-conduction tubing (7, fig. 4, left) this carotid tracing shows lag of 0.01 second.

A. Pulmonary artery in a normal. Note that »take-off» (at onset of ejection) of pulmonary artery tracing precedes corresponding point on carotid tracing by 0.03 second. Correcting for lag in carotid pulse recorder, »PAc interval» becomes + 0.02 second for this individual. In a series of normals the PAc interval varied from + 0.03 to — 0.01 second.

B. Ascending aorta in a normal.

C. Pulmonary artery in a case of left bundle-branch block, showing PAc interval of + 0.07 second (0.04 second beyond limit of normal variation).

D. Pulmonary artery in a case of right bundle-branch block, showing PAc interval of — 0.03 second (0.02 second beyond limit of normal variation).

E. Left ventricle in a case of myocardial infarct. Note that left border of silhouette remains in an almost stationary, diastolic position throughout all of systole, then collapses when pressure falls at beginning of diastole.

ventricular wall may be replaced by varying degrees of limitation of motion, absence of motion or reversal of motion; and not infrequently a characteristic »falling inward» of the weakened ventricular wall is seen during early diastole.

In this paper an attempt to illustrate all of the possible applications of electrokymography would be out of place. However, it may be permissible to call attention to the fact that excellent tracings have been obtained of such phenomena as the cyclic changes in roentgen-ray transmission through the lung parenchyma, due to the »capillary pulse» of the lung. And by discarding the bit of fluorescent screen that is usually placed at the »window» of the multiplier phototube, and substituting a pocket flashlight for the roentgen beam, excellent plethysmographic tracings have been obtained of finger pads (by transmitted light) and superficial skin vessels over various body surfaces (by back-scatter of incident light).

Comment. — The question naturally arises, »Will roentgen electrokymography supplant its earlier counterpart, roentgen kymography? Experience thus far suggests that this will not occur and that actually the two methods are complementary rather than competitive. Roentgen

kymography produces valuable records of motion at many points on the cardiovascular silhouette, on a single film. Electrokymography supplements such records by facilitating the accurate analysis of the motion at selected points; the ease with which other phenomena (heart sounds, pulse tracings, E. K. G.) are simultaneously recorded on the same time axis with the electrokymogram, is especially helpful. We have the impression that roentgenologists who have had extended experience with roentgen kymography will be quick to take up the newer method, and experience with the electrokymograph will probably increase the demand for the older device.

SUMMARY

The roentgen electrokymograph utilizes significant fluctuations in the fluoroscopic roentgen beam, to produce graphic records of such physiologic phenomena as the pumping action of the heart and the capillary pulse of the lung parenchyma. This new device consists of a clinical fluoroscope, a 931-A (or equivalent) multiplier phototube with its necessary power supply, a selective »filter» to absorb the alternating current »ripple» in the roentgen beam while passing the significant current fluctuations that are to be recorded, some form of recording galvanometer, and means for the simultaneous registration of some such time-reference curve as the carotid sphygmogram, an oscillogram of the heart sounds or an electrocardiogram. The apparatus is described in sufficient detail so that the reader may build it for himself. Records are shown, of ventricular motion, including a case of myocardial infarct, and of aortic and pulmonary artery pulsations, including cases of right and left bundle-branch block. A basis for interpretation of electrokymograms is outlined.

ZUSAMMENFASSUNG

Der Röntgenelektrokymograph verwendet die signifikanten Schwankungen der fluoroskopischen Röntgenstrahlen zur Erzielung einer graphischen Darstellung solcher physiologischer Erscheinungen wie der Pumptätigkeit des Herzens sowie des Kapillarenpulses des Lungenparenchyms. Diese neue Apparatur besteht aus einem klinischen Fluoroskop, einer 931-A (oder gleichwertigen) vervielfältigenden Aufnahmeröhre mit ihrer erforderlichen Kraftzufuhr, einem selektiven »Filtrum», das die entgegengesetzte »Stromwelle» der Röntgenstrahlen absorbiert, während es die zu registrierenden signifikanten Stromschwankungen durchlässt, irgend einer Art aufzeichnendem Galvanometer sowie Anordnungen zur gleichzeitigen Registrierung von einer zeitlich gleichgeordneten Kurve, wie z. B. dem Karotissphygmogramm, einem Oszillogramm der Herztöne oder einem Elektrokardiogramm. Der Apparat wird so eingehend beschrieben, dass der Leser ihn selbst konstruieren kann. Es werden Aufzeichnungen der Herzkammertätigkeit gegeben, darunter ein Fall von Herzmuskelinfarkt, sowie von Aorten- und Pulmonalarterienpulsationen, darunter auch Fälle von rechts- und linksseitigem Schenkelblock. Ein Prinzip zur Interpretierung des Elektrokymogramms wird skizziert.

RÉSUMÉ

L'»électrokymographe Roentgen» utilise les fluctuations caractéristiques du faisceau des Rayons Roentgen sur l'écran fluorescent pour obtenir des enregistrements graphiques de phénomènes physiologiques tels que le travail de pompage du cœur et le pouls capil-

laire du parenchyme pulmonaire. Ce nouvel agencement est constitué par un fluoroscope de clinique, un phototube multiplicateur 931-A (ou son équivalent) avec la source d'énergie nécessaire, un »filtre» sélecteur destiné à absorber la »ride» alternative du courant dans le faisceau de Rayons Roentgen lorsqu'il traverse les fluctuations caractéristiques du courant qu'il s'agit d'enregistrer, un galvanomètre enregistreur d'un type ou d'un autre, et enfin le nécessaire pour tracer simultanément quelque courbe donnant l'indication des temps, par ex., celle d'un sphygmogramme carotidien, d'un oscillogramme des bruits du cœur ou d'un électrocardiogramme. L'appareil est décrit avec assez de détails pour que le lecteur puisse le construire lui-même. Reproduction d'enregistrements de tracés des mouvements du ventricule (comprenant aussi un cas d'infarctus du myocarde) et de ceux des pulsations de l'aorte et de l'artère pulmonaire (avec des cas de blocage de la branche droite et de la branche gauche du faisceau). Esquisse du principe d'interprétation des électrokymogrammes.

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FROM THE ROENTGENDIAGNOSTIC DEPT. OF SAHLGRENSKA SJUKHUSET, GOTHENBURG, SWEDEN (CHIEF: DR. GÖSTA RUNSTRÖM).

THE SIX-FRAME TRANSLUMINATION CABINET[1]

by

Gösta Runström

Owing to the ever increasing number of examinations in the roentgen departments of our hospitals and the resulting increase of the number of films, it has proved difficult to obtain, in the premises now available for the purpose, sufficiently large translumination spaces for the examination and demonstration of roentgen films. In order to overcome these difficulties, to some extent at least, double frames have been constructed, which can be pushed up and pulled down in front of the illuminated window, whereby twice as many films may be shown at a time in the translumination cabinet. BAASTRUP has further increased the capacity of the cabinet by hanging up in front of it five frames which may be pulled down in turn before the illuminated window. This contrivance, however, has the disadvantage that the frames must be placed at different distances from the translumination window. With a view to eliminating the difficulties just mentioned, I have had a translumination cabinet constructed according to the following principles.

The contrivance (Fig. 1) consists of a translumination cabinet *a* and a working table *b*. A device *c* for shifting six film frames is fixed above the table. The dimensions of the translumination window of the cabinet is 1300 × 975 millimetres and consists of an opal glass pane, behind which there are three luminous tubes supplying an evenly distributed light. Further, there is at the bottom of the cabinet a similar tube fixed in a reflector and provided with a particular switch. By means of a lever *d* this tube may be raised to a position close behind the lower opal glass window, which is about 18 centimetres high, whereby a more intensely illuminated space is obtained, particularly convenient for examining pictures of ears, sinus films etc. If the reflector is moved backwards, an increased, even illumination of the whole window is achieved. It is of great importance when translumination films are to be read that the

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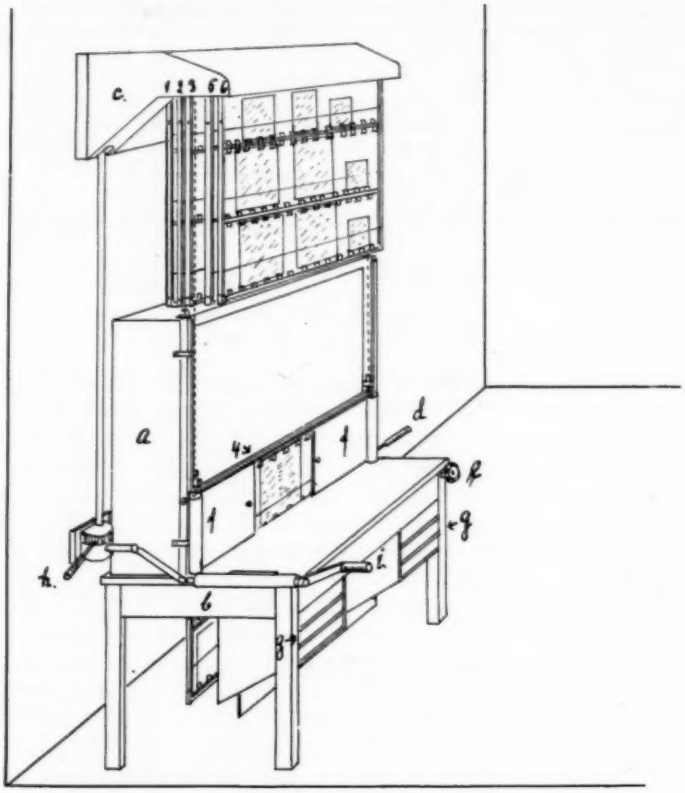

Fig. 1.

part of the window which is not covered by the film should be darkened, as the light radiating from this part considerably diminishes the ability of the eye to observe details. This excessive light is also unnecessarily tiring to the eye. Physicians often pay too little attention to this. This arrangement of darkening, however, was already used many years ago in the small translumination cabinets constructed by FORSSELL.

In the cabinet now described this darkening is achieved partly by means of a curtain close behind the opal glass window, which curtain may be raised or lowered by a wheel *e* to the right at the front of the working table, partly by two curtains *f* in front of the film frame, which are movable towards the centre of the window. Thus variable diaphragms for the examination of details may be arranged in a convenient way

The working table contains three drawers. Under the table there are hutches *g* on either side with three shelves each, on which may be placed transmissions from other departments of the hospital, films for each frame etc.

In the shifting device *c*, which is fastened to the wall above the translumination cabinet, there are six numbered frames for the hanging up of films. By a gear-lever *h* on the left end of the table a film frame may be moved to the window in front of the translumination cabinet, irrespective of its number. The film is seized by a clutch fixed to a chain running over a gear-wheel.

By means of a handle *i* to the left of the long side of the table the frame is conducted downward and then seized by a pair of ledges on each side of the translumination window.

The frame is divided into three horizontal spaces for the hanging up of the film. By the handle the film may be easily managed with the left hand to the right level, whereas the curtain — which can be raised or lowered — is handled with the right hand. In order to avoid the risk of the operator's breaking the glass pane of the frame by kicking it with his feet when the frame is lowered to its bottom position for the examination of the films in its upper spaces, there is a kicking shelter in front of the frame under the table.

The device for the examination of films described above seems to me the most suitable one for a roentgen department with limited space. For larger departments a combination with cabinets of the ordinary type or the two-frame type is to be preferred, as, in some cases, these latter types afford a better survey of the films.

As in hospitals rounds mostly start in the roentgen department, it has proved very suitable to hang the film material in a six-frame cabinet, for, as a rule, it is quite sufficient for a clinic.

If the six-frame cabinet is used, it is possible for the roentgen physician to show the whole material sitting comfortably beside the head physician of the clinic, and the attendant assistants standing behind can thus see the films clearly.

Further I have found the cabinet very useful for teaching roentgendiagnostics. The six-frame cabinet will suffice for a whole lecture and offers the students exceedingly good chances of following the examination of the film material from a short distance.

This cabinet may be ordered from AB Svenska Philips, Gothenburg, Sweden.

SUMMARY

The author describes a translumination cabinet arrangement where six frames can be pulled up and pushed down thus increasing the capacity.

ZUSAMMENFASSUNG

Verf. beschreibt einen Lichtschrank, wo durch eine Wechselanordnung 6 Filmrahmen vor den Lichtschrank heruntergeschoben werden können, wodurch die Kapazität vermehrt wird.

RÉSUMÉ

L'auteur décrit un négatoscope où, grâce à un système d'escamotage, on peut abaisser 6 porte-films devant l'appareil, augmentant ainsi le rendement.

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